4D Flow MR Imaging of the Left Atrium: What is Non-physiological Blood Flow in the Cardiac System?

Tetsuro Sekine1*, Masatoki Nakaza2, Mitsuo Matsumoto3, Takahiro Ando4, Tatsuya Inoue5, Shun-Ichiro Sakamoto6, Mitsunori Maruyama7, Makoto Obara8, Olgierd Leonowicz9, Jitsuo Usuda5, and Shinichiro Kumita2

Most cardiac diseases cause a non-physiological blood flow pattern known as turbulence around the heart and great vessels, which further worsen the disease itself. However, there is no consensus on how blood flow can be defined in disease conditions. Especially, in the left atrium, the fact that vortex flow already exists makes this debate more complicated. 3D time-resolved phase-contrast (4D flow) MRI is expected to be able to capture blood flow patterns from multiple aspects, such as blood flow velocity, stasis, and vortex quantification. Previous studies have confirmed that physiological vortex flow is predominantly induced by the higher-volume flow from the superior left pulmonary vein. In atrial fibrillation, 4D flow MRI reveals a non-physiological blood flow pattern, which information may add value to well-established clinical risk factors. Currently, the research target of LA analysis has also widened to lung surgeons, pulmonary vein stump thrombosis after left upper lobectomy. 4D flow MRI is expected to be utilized for many more variable diseases that are currently unimaginable.

Keywords: cardioembolism, computational fluid dynamics, left upper lobectomy, stasis, vorticity

Introduction

What is the non-physiological blood flow pattern?

Time-resolved phase-contrast (4D flow) MRI has been clinically implemented in this decade owing to advances in MRI scanners and post-processing software.1–6 4D flow MRI enables the visualization of various blood flow patterns, such as jet and vortex flow, and to derive various quantitative parameters, such as blood flow volume, wall shear stress, and energy loss.4,5,7,8 As a generalized statement, most cardiac diseases cause a non-physiological blood flow pattern known as turbulence around the heart and great vessel, which further worsens the disease itself.9,10 Although the term turbulence is easy to understand, its definition has not yet been determined. There is no consensus to distinguish blood flow in disease conditions from physiological blood flow patterns. In the cardiac system, vortex flow and jet flow are sometimes considered indicators of turbulence. However, this flow pattern is often observed even in healthy subjects, for example, vortex flow in the heart chamber, and jet and vortex flow around the ascending aorta.4 In this study, we present the physiological and non-physiological blood flow pattern in the left atrium (LA), which is a good target to discuss this topic.

Physiological flow pattern in the left atrium

In the year 2000, Nature first published the phase-contrast-MRI-based 3D-volumetric cardiac flow pattern visualized by Kilner et al.11 One of the key findings of this study is that physiological rotational flow is induced by the asymmetric and curvatures of the looped heart (Fig. 1). The physiological-vortex flow has the potential to minimize energy dissipation in the cardiac system by maintaining kinetic energy...
The next year, this blood flow pattern was confirmed using a similar method by the Linköping group, which is one of the leading research groups in the 4D flow MRI field. Their evaluation focusing on LA blood flow showed that vortical flow in the LA originated predominantly from the flow via the left pulmonary veins, followed by its collision with the flow via other pulmonary veins (Fig. 1). They concluded that this physiological vortex flow pattern may have beneficial effects in avoiding LA blood flow stasis in addition to kinetic energy preservation. The vortex flow leads to a relatively high-velocity flow close to the atrial wall. It may have washing and rinse effects, resulting in the prevention of thrombosis. In healthy subjects, depending on age, the duration of vortex flow decreases with slower velocity (< 30 years vs. > 50 years; duration of vortex flow during systole 178 ± 63 vs. 124 ± 44 ms, and peak velocity 54 ± 12 cm/sec vs. 41 ± 11 cm/sec). This tendency was observed regardless of heart rate or ejection fraction. This age-related change was derived from the myocardial structural changes and Ca²⁺ channel handling differences, sympathetic nervous system alteration, and a reduction in arterial compliance and endothelial function. Decreasing vortex flow has also been observed in various heart diseases. Suwa et al. recruited 32 patients with or without organic heart diseases. The patients without vortex flow had a higher tendency of organic heart disease compared to those with vortex flow (92% vs. 30%). The enlargement of LA volume significantly correlated with the diminishing vortex flow formation (56 ± 17 vs. 39 ± 14 ml), but the odds ratio was very small (0.92 [95% confidence interval 0.86–0.99]). In contrast, the systolic peak of maximal volume in the left superior pulmonary vein (LSPV) was significantly lower without minimal overlap in the patients with vortex flow (32.8 [25.7–54.1] vs. 58.6 [52.3–82.4] ml/sec). Interestingly, the morphological difference, the cross-sectional area of the pulmonary vein, did not differ significantly between patients with and without vortex flow. Another interesting point was that no significant blood flow change was observed in the other three pulmonary veins (the left inferior pulmonary vein and two right pulmonary veins).

In summary, vortex flow is the physiological flow pattern in the LA. It is predominantly induced by high-velocity flow via the LSPV. Both aging and various heart diseases hamper this physiological flow pattern with minimal morphological changes. In this context, 4D flow MRI may be more sensitive than other conventional cardiac CT or MRI in terms of capturing earlier changes in the alteration of LA function. In the next sections, we present two target diseases in which non-physiological blood flow patterns in the LA contribute to disease conditions, more specifically, arterial fibrillation (AF) and post-lung cancer surgery. Table 1 represents the summary of previous studies.

### Basic Concepts of 4D Flow MRI Assessment of Left Atrium

#### 4D flow MRI acquisition targeting the left atrium

One of the difficulties of 4D flow MRI scans in AF is non-sinus triggering. Since the sampling during 4D flow MRI is based on electrocardiogram (ECG) synchronization, the data might be severely compromised by beat-to-beat variation. Markl et al. performed a novel simulation study to test the reliability of phase-contrast MRI in patients with cardiac arrhythmia. They acquired real-time in vivo Doppler transesophageal echocardiography (TEE) data from five patients with AF as input information. From these TEE data, they generated simulated phase-contrast MRI consisting of magnitude and velocity-encoding phase images. Furthermore, based on these images, the MR k-space data were calculated using Fourier transformation. Through this process, the simulated k-space data corresponding to multiple RR-intervals spanning...
Table 1  Summary of the previous 4D Flow MRI studies which evaluated left atrium blood flow

| Year | Journal | Group | Basic/ clinical research | Healthy participants | Paroxysmal AF | Persistent AF | MRI machine# | Magnet strength# | Scan Acceleration# | Voxel size (mm) # | Heart phase (reconstructed)† | VENC (cm/sec) | Acquisition time (min) |
|------|---------|-------|--------------------------|----------------------|---------------|---------------|--------------|-----------------|--------------------|------------------|-------------------------|----------------|------------------------|
| 2013 | JMRI    | Northwestern University | Clinical            | 19                   | 6             | 4             | Siemens-Avanto and Trio | 1.5T and 3.0T  | Not specified | 2.5 x 2.5 x 2.8 | 26               | 100-150                | 15-25              |
| 2015 | JCAT    | Northwestern University | Basic                | 4                    |               |               | Siemens-Aera, Avanto and Espree | Simulation | Simulation | 2.5-3.0 x 3.0 | 24-27             | 100-150                | 18-12              |
| 2016 | Int J Cardiovasc Imaging | Northwestern University | Clinical            | 8                    | 33            | 29            | Siemens-Aera, Avanto and Skyra | 1.5T and 3.0T  | GRAPPA R = 2 | 2.5-3.0 x 3.0 | 24-26             | 100-150                | 20-10              |
| 2016 | Circulation-CI | Northwestern University | Clinical            | 15                   | 30            | 30            | Siemens-Aera, Avanto and Skyra | 1.5T and 3.0T  | GRAPPA R = 2 | 2.5-3.0 x 3.0 | 24-26             | 100-150                | 20-10              |
| 2016 | EHJ-CI  | Northwestern University | Clinical            | 30                   | 40            | -             | Siemens-Avanto and Skyra | 1.5T and 3.0T  | Not specified | 2.5-3.0 x 3.0 | Not specified | 100-150                | 20-10              |
| 2016 | Invest Radiol | Northwestern University | Clinical            | 30                   | 42            | 39            | Siemens-Aera, Avanto and Skyra | 1.5T and 3.0T  | GRAPPA R = 2 | 2.5-3.0 x 3.0 | 24-26             | 100-150                | 20-10              |
| 2017 | Front. Physiol | Linköping University | Clinical            | -                    | -             | 14            | Philips-Ingenia | 3.0T | SENSE R=3 | 2.8 x 2.8 x 2.8 | 40               | 120                    | Not specified |
| 2019 | JMRI    | University of Calgary | Clinical            | 15                   | 45            | -             | Siemens-Skyra | 3.0T | Not specified | 2.0-3.6 x 2.0-3.0 | 15-20           | 150-200               | 15-10              |
| 2019 | Front. Physiol | Linköping University | Clinical            | -                    | 10            | -             | Philips-Ingenia | 3.0T | SENSE R = 3 | 2.8 x 2.8 x 2.8 | 40               | 120                    | Not specified |
| 2020 | Int J Cardiovasc Imaging | Baker Heart and Diabetes Institute | Clinical            | 18                   | 91            | -             | Siemens-Prisma | 3.0T | Not specified | Not specified | Not specified | Not specified |
| 2021 | JCMR    | University of Oxford | Basic               | 14                   | 64            | 22            | Siemens-Verio | 3.0T | GRAPPA R =3 | 2.4 x 2.4 x 2.5-3.0 | 20-30           | 110-120               | 5-20               |
| 2021 | JMRI    | Northwestern University | Basic               | -                    | -             | 25            | Siemens-Magbeton | 1.5T | 3D radial | 2.5 x 2.5 x 2.5 | 27               | 150                    | 8-48               |
| 2021 | Scientific reports | Vrije Universiteit Amsterdam | Clinical            | 5                    | 10            | -             | Siemens-Avanto | 1.5T | GRAPPA R = 2 | 3.1 x 3.1 x 3  | 31               | 100                    | 15-20              |

(Continued)
### Table 1 (Continued)

| Year | Journal | Group | Basic/clinical research | Healthy participants | Paroxysmal AF | Persistent AF | MRI machine# | Magnet strength# | Scan Acceleration# | Voxel size (mm)# | Heart phase (reconstructed)† | VENC (cm/sec) | Acquisition time (min) |
|------|---------|-------|-------------------------|----------------------|---------------|--------------|--------------|----------------|------------------|----------------|--------------------------|----------------|-------------------------|
| 2021  | Appl. Sci. | University of Calgary | Clinical | 24 | 108 | 40 | Siemens-Skyra | 3.0T | Not specified | 2.0–3.5 × 2.0–3.5 × 2.5–3.5 | 25 | 150–200 | 8–12 |
| 2021  | Wellcome | University of Sheffield | Clinical | 10 | - | 8 | Philips-Ingenia | 1.5T | EPI R = 5 and SENSE R = 2 | Not specified | 30 | 150 | Not specified |

| Year | Journal | Group | Basic/clinical research | Healthy participants | LUL without thrombosis | LUL with thrombosis | Other lung lobectomies | MRI machine# | Magnet strength# | Scan Acceleration# | Voxel size (mm)# | Heart phase (reconstructed)† | VENC (cm/sec) | Acquisition time (min) |
|------|---------|-------|-------------------------|----------------------|----------------------|----------------------|-------------------------|--------------|----------------|------------------|----------------|--------------------------|----------------|-------------------------|
| Post lung surgery |  | | | | | | | | | | | | |
| 2020  | MRMS | Nippon Medical School | Clinical | 8 | 1 | - | - | Philips-Achieva | 3.0T | k-t PCA R = 8 | 1.75 × 1.75 × 2.0 | 24 | Dual VENC (50 and 150) | 12 |
| 2021  | MRMS | Nippon Medical School | Clinical | 8 | 10 | 8 | - | Philips-Achieva | 3.0T | k-t PCA R = 8 | 1.75 × 1.75 × 2.0 | 24 | Dual VENC (50 and 150) | 12 |
| 2021  | J Thorac Dis | Kagoshima University | Clinical | - | 11 | 2 | 27 | Siemens-Aera and Prisma | 1.5T and 3.0T | GRAPPA R = 3 | 2.0 × 2.0 × 2.5 | 13 | 100 | 11 |

* The authors guess that the study from the Northwestern group published around 2016 may have some extents of overlap of patients, but it was not specified.
* If the various machines/sequences were used, we extracted the representative one.
† If the reconstructed heart phase was not specified, it was calculated from the temporal resolution when heart rate = 60.
AF, atrial fibrillation; LUL, left upper lobectomy.
several heartbeats were successfully generated (Fig. 2). Fortunately, the simulated phase-contrast MRI data were almost the same as the averaged TEE data during acquisition (Fig. 3). Despite the beat-to-beat variation, the quantified mean velocity did not differ significantly between the two modalities within < 10% error. Care should be taken that the real 4D flow MRI acquisition may omit some of the data due to beat-to-beat variation because arrhythmia rejection is generally combined to avoid triggering via amplified noise. Another group from the University of Oxford explored test–retest reproducibility in patients with AF and sinus rhythm. They recruited 85 subjects consisting
of 64 with paroxysmal AF, 22 with persistent AF, and 14 healthy subjects. The coefficient of variation for the interval scan (30 [27–35] days) ranged from 7% for peak velocity and vorticity to 14% for stasis. The LA peak velocity and vorticity were the most temporally stable flow parameters, irrespective of changes in heart rate, blood pressure, and differences in heart rhythm. Unexpectedly, the interval-scan flow parameters tended to be smaller in persistent AF than in sinus rhythm.

To investigate the variation in blood flow induced by arrhythmic heartbeats in more detail, the Northwestern group currently proposed a fully self-gated free-running 5D flow framework (4D flow plus RR-interval variation domain), which was expanded from the currently developed another 5D flow scan scheme (4D flow plus respiratory variation domain) (Fig. 4).20–22 In patients with arrhythmia, the averaged flow pattern may have several velocity peaks. For example, if a patient has two R-R variations due to arrhythmia, 800 ms and 1200 msec, the averaged blood flow curve has two peaks corresponding to each R-R variation. Since 5D Flow can separate the velocity profile corresponding to each R-R interval, the extracted data may be more sensitive in detecting altered LA conditions.22 Although it did not reveal statistically significant differences between R-R resolved and R-R averaged flow parameters, this approach is very promising due to the capability of depicting flow information that is impossible to achieve with other methods.

**4D flow MRI evaluation for left atrium**

Visual evaluation should be performed before any quantitative measurements because the net velocity or secondary velocity profile (e.g., vorticity) can be easily changed by multiple factors, including scan parameter differences, unrecognized artifacts, inevitable error of segmentation, and variations of post-processing steps. In general, 3D pathline views emitted from each pulmonary vein or whole LA can be used to capture the blood flow patterns briefly (Fig. 1). As described in the previous sections, the vortex flow mainly derived from the LSPV is a physiological blood flow pattern.

For a more detailed and objective analysis, several flow parameters are calculated from the velocity data. Most of these parameters are derived from the volume average of all voxels included in the LA. Therefore, the intra- and inter-variability of LA segmentation may be problematic. Fortunately, several studies have already revealed that the effects of these variabilities on flow parameters are limited to 10%.13,19,23–25 Most studies utilized 3D PC-MRA data generated from 4D flow MRI as the reference data for segmentation. It may minimize misregistration between flow data and segmentation data despite its low spatial resolution (i.e., > 2 mm voxel size) compared to utilizing other images such as cine-MRI and contrast-enhanced MRA. Note that LA volume, which affects the flow pattern, can also be measured through this step.16,23,25,26 Interestingly, the correlation between the flow profile and left ventricular ejection fraction...
has not been observed, although the clinical risk-scoring system, namely, the CHADS2 score or its additional risk-scoring system, CHA2DS2-VASc score, includes this factor (i.e., heart failure).\textsuperscript{16,25,27}

More specifically, the parameters listed below were used in the evaluation. These values can be calculated as single- or time-averaged data. There is no consensus about which timing during the cardiac cycle best reflects the disease
condition. While one study indicated the early-diastole phase, other studies reported the late-diastole phase.

Peak velocity
The definition of peak velocity differs among studies. It is the maximum velocity in each voxel during the R-R interval or the top several percentages (e.g., 5%) among the voxels. The former parameter may reflect pulsatility, and the latter may be robust to errors derived from segmentation and background error.

Mean and median velocity
Note that the velocity distribution is not normally distributed but skewed left with a longer right tail. Therefore, there was a significant difference between the mean and median velocities.

Stasis
It is the ratio of the total number of cardiac time frames (n) with a velocity below the threshold to the total number of frames (NTot). Based on the sensitivity analysis to differentiate controls, paroxysmal AF, and persistent AF, 10 cm/s is usually used as the threshold (Fig. 5). This threshold is lower than that used in the TEE study (20 cm/s) because 4D flow MRI underestimates velocities due to lower spatiotemporal resolution.

Time-to-peak
The timing of high LA flow velocities with respect to the beginning of the cardiac cycle was defined by the R-wave. Only one study utilized this parameter, which might not be useful in describing the disease condition.

Residence time distribution
A virtual particle seeding plane is created in a specific pulmonary vein. The exit plane is located at the mitral valve. The degree of particles that did not cross the exit plane was calculated by combining the number of particles and time-domain information. This concept has already been validated in the LV chamber and may be a novel marker to represent the blood function of the LA. However, only one study utilized this factor, and its clinical association was not distinct.

Vortex
The volumes of the largest vortex rings inside the LA were calculated using the lambda2 ($\lambda^2$) value over the cardiac cycle. A specific lambda threshold for vortices was defined (e.g., half the mean $\lambda^2$ value over the cardiac cycle). The time-averaged vortex volume and peak vortex volume within the systole and diastole were...
measured. The volume-averaged and time-averaged magnitude of vorticity (radian) can also be calculated. It should be noted that this method can only detect larger-scale vortices over the voxel resolution of 4D flow MRI (e.g., > 2 mm).

4D Flow MRI Assessment of Atrial Fibrillation

The clinical background of atrial fibrillation
AF is a common disease among older subjects. In the Framingham Heart Study population, the lifetime risk of AF was estimated to be 37.0% after the age of 55 years. This disease condition contributes to adverse fatal outcomes by increasing the incidence of cardioembolic stroke. To prevent stroke, anticoagulation therapy is the first-line treatment; however, the trade-off with the side effects of the drug, i.e., bleeding, needs to be considered. Therefore, risk stratification of coagulation is usually performed based on the clinical risk-scoring system, CHADS2 score or CHA2DS2-VASc score. Although the treatment strategies for AF have been validated in various ways, there still remain areas of uncertainty, such as the effect of treatment options to maintain sinus rhythm on the overall risk and the safe strategies for determining whether low-risk patients can discontinue anticoagulation. Further risk stratification is required.

The current risk factor scoring, the CHA2DS2-VASc score, consists only of clinical factors, such as age, sex, history of heart failure, history of hypertension, history of stroke, history of vascular disease, and history of diabetes. In addition to these clinical factors, direct risk stratification for coagulation based on the blood flow profile has been investigated. Previous studies have utilized TEE, a common clinical approach for AF, and revealed that low flow in the LA and left atrial appendage (LAA) predicts the risk of thromboembolic events. The drawbacks of TEE are its invasiveness and 2D acquisition, which do not cover the entire volume of the LA. As an alternative method, 4D Flow MRI is expected to be useful because it enables non-invasive 3D-volume acquisition.

Clinical studies of 4D flow MRI in atrial fibrillation
In 2013, the Northwestern group first reported a detailed LA flow pattern in AF. They measured the blood flow velocity of each voxel over the cardiac cycle in the LA. They revealed three trends in LA blood flow. First, the younger healthy volunteers had a significantly wider range of velocity distribution with a higher velocity in the LA compared to healthy older participants. Second, patients with paroxysmal AF had a velocity profile similar to that of age-matched healthy participants. Third, compared to healthy volunteers, patients with AF had larger changes in velocity angles, which may correspond to non-physiological flow. In their study, they presented only a preliminary result in four cases of persistent AF.

In accordance with this preliminary study, the same group published four papers comparing volunteers, paroxysmal AF, and persistent AF around 2015. They published an informative paper focusing on detailed flow parameters to distinguish non-physiological blood flow patterns from physiological ones. They recruited 30 healthy volunteers, 42 with paroxysmal AF and 39 with persistent AF, and evaluated stasis, peak velocity, and time-to-peak metrics. They also evaluated global (all voxels in the LA) and regional (2 voxels inward from the outer LA boundaries) flow metrics of the LA.

In their study, they performed a sensitivity analysis to identify the threshold for LA stasis and LA peak velocity. The threshold ranging from 10 to 18 cm/sec in LA stasis robustly differentiated between all group differences (young controls vs. old controls, age controls vs. paroxysmal AF, age controls vs. persistent AF, and paroxysmal AF vs. persistent AF) (Fig. 5). Care should be taken that this threshold is relatively lower than that reported in the TEE study (20 cm/s). In the velocity threshold for utilizing the % of the top LA velocity ratio, there is no robust point; however, 5% is sub-optimal (Fig. 5). In the comparison between regional and global metrics, there was a tendency of higher stasis with slower flow around near-wall regions in both the healthy and AF groups. It might be an unexpected result that the diminishing vortex flow in AF does not cause a more distinct velocity profile difference between the center and peripheral regions in the LA. The reduced mean and peak velocities were related to age and LA volume but not to the heart rate.

In another study, they discussed the relationship between 4D flow MRI metrics and standardized clinical risk factors, CHA2DS2-VASc scores. In this study, the flow parameters were calculated for each single time-point (i.e., systole, early diastole, and mid-late diastole) and time-averaged. The difference in flow profile was pronounced in the data at early diastole and during the entire RR. The mean, median, and peak velocity at early diastole correlated slightly with the CHA2DS2-VASc scores (r = –0.33 to –0.368). The authors emphasized that substantially different LA velocities despite similar clinical scores indicate the added value of 4D flow-deriven information. To confirm this hypothesis, further longitudinal clinical studies are needed as described by the authors.

They also evaluated the correlation of blood flow patterns between right atrium (RA) and LA blood flow. In the study, both RA and LA had a tendency of lower blood flow velocity with a higher ratio of stasis in both the patients with paroxysmal AF and persistent AF than in the healthy group. The correlation between LA and RA flow parameters was high (mean velocity: r = 0.64, stasis: r = 0.55). There was no systematic difference between the LA and RA flow velocity profiles. Further delineation of clinical and/or blood flow factors needs to be sought to explain the more prevalent systemic versus pulmonary thromboembolism in patients with AF.

Among studies described above have focused on the blood flow pattern in the LA, not specifically in the LAA where thrombosis formation occurs most commonly. In
another previous study authored by the Northwestern group, both LA and LAA blood flow characteristics were evaluated in a similar way to the one described above. In all healthy control subjects (n = 15), LAA mean and peak velocities consistently decreased by 21% and 12%, respectively, and increased LAA stasis (< 10 cm/s) by 58%. However, this trend was diminished in both paroxysmal AF and persistent AF (Fig. 6). The flow parameter in LA had a stronger relationship with the CHA2DS2-VASc scores than the LAA. However, even for AF patients with higher scores (CHA2DS2-VASc scores of ≥ 3), 11% to 54% had flow parameters that were within normal ranges. As a sub-study, the agreement of LA-velocity and LAA-velocity between 4D flow MRI and clinical reference standard TEE was performed in 30 patients. A modest relationship was observed (peak velocity r = 0.41, stasis-related parameter r = -0.39).

The Calgary group recruited 45 paroxysmal AF patients and evaluated the vortex in addition to velocity parameters in the LA. The results show that predominant blood flow from the LSPV was observed even in paroxysmal AF patients with only a minor reduction in peak velocity. Unexpectedly, the vortex volume in paroxysmal AF patients was 74% higher than that in healthy controls. They confirmed the discrepancy between CHA2DS2-VASc risk score and blood flow profiles evaluated by 4D flow MRI, which was similar to a previous study. After multivariate analysis, there was no measurable parameter associated with the CHA2DS2-VASc risk score, except for age.

**Clinical studies of 4D flow MRI after electrical cardioversion for atrial fibrillation**

The Linköping group reported a change in blood flow after electrical cardioversion. They recruited 14 patients and performed 4D flow MRI at two time-points: 2–3 hours (Time-1) and 4 weeks (Time-2) following cardioversion. As a novel point of the analysis, they performed non-rigid registration from all time frames to the early-diastolic time frames based on PC-MRA images. In addition, vorticity calculation and the definition of stasis-threshold as 15 cm/s and not 10 cm/s were applied. In the late-diastole phase, the velocity parameters and vorticity generally increased, and the stasis-related parameter decreased from Time-1 to Time-2. There was a strong correlation between the thrombin–antithrombin complex and the volume of stasis (r² = 0.69).

The Calgary group recruited 172 subjects consisting of 108 in the pre-ablation cohort, 40 in the post-ablation cohort, and 24 healthy controls. In this study, the mean LA flow...
The clinical background of post-lung surgery

In patients undergoing lung cancer surgery, the incidence of stroke is approximately 1% and five times higher than that in patients who did not undergo surgery.\textsuperscript{44,45} In this cohort, pulmonary vein stump thrombus formation (PVST) sometimes occurs with a higher prevalence after left upper lobectomy (LUL).\textsuperscript{46,47} This relationship with cerebral or other infarctions in other organs was originally reported by several Japanese researchers.\textsuperscript{46–49} Following these studies, the same disease entity has been reported in other countries.\textsuperscript{44,50,51} Currently, a Japanese multicenter study evaluating 1040 patients was conducted.\textsuperscript{52} Among 1040 patients, postoperative contrast-enhanced CT scans (median duration of 3 days after the operation) confirmed PVST in 127 (12.2%) patients. After the multivariable analysis, left-sided pulmonary resection had the highest odds ratio (3.861 [2.127–6.711]) among all clinical and operation-related factors. Another meta-analysis also confirmed that LUL
**Fig. 9** Collision pattern of blood flow in the patients without thrombosis after left upper lobectomy. The left atrium and ventricle were segmented as yellow translucent VOIs. Each colored pathline represents blood flow from each pulmonary vein (light blue, RSPV flow; blue, RIPV flow; light green, LIPV flow). The time order is from **a** to **d**. In this figure, the LIPV flow and RSPV flow collide with each other in **c** and flow to the mitral valve in **d**. The 2D overlay view shows clear collision of the flow from the right superior and left inferior pulmonary veins at the diastolic phase (arrow in **e**). The merged blood flow becomes the driving force behind the formation of the vortex flow in the left atrium (arrowheads in **e**). The velocity-weighted map more clearly depicts high velocity on and around inflow from the pulmonary vein (arrows in **f**), which gradually distributes to the remaining areas of left atrium (arrowheads in **f**). LIPV, left inferior pulmonary vein; RIPV, right superior pulmonary vein; RSPV, right superior pulmonary vein. This figure was reused from a published paper with permission.58

**Fig. 10** No collision pattern of blood flow in the patients with LSPV stump thrombus and cerebral infraction 4 days after left upper lobectomy. Cerebral infraction was followed by MRI scan, and LSPV stump thrombus was followed by contrast-enhanced CT scan. LSPV thrombus disappeared when 4D flow MRI was performed. The left atrium and ventricle were segmented as yellow translucent VOIs. Each colored pathline represents the blood flow from each pulmonary vein (light blue; RSPV flow, blue; RIPV flow, light green; LIPV flow). The time order is from **a** to **d**. In this figure, the flow does not collide and dissipate to the left atrium wall. The 2D overlay view shows that the flows from the right superior and left inferior pulmonary veins pass each other at the diastolic phase (arrow in **e**). The velocity-weighted map acknowledges the slow flow areas where blood flow has been left out (arrowheads in **f**). Note that the velocity scale is the same as that in Figure 10-**e** and **f**. LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right superior pulmonary vein; RSPV, right superior pulmonary vein. This figure was reused from a published paper with permission.58
had a higher likelihood of PVST.\textsuperscript{53} As one of the promoters of PVST, cancer-related coagulation has been considered.\textsuperscript{54} This theory was disproved by a large nationwide study.\textsuperscript{44} They recruited 20624 subjects who underwent pneumonectomy and lobectomy. In this study, a detailed comparison between lung cancer with and without surgery, or lung cancer with pneumonectomy/lobectomy and with wedge resection, was performed to exclude the bias from other risk factors, such as cancer itself, a higher burden of comorbidity, and lifestyle. Their results confirmed that pneumonectomy/lobectomy was independently associated with the development of stroke, regardless of AF. PVST sometimes causes infarction in several organs, especially the brain (around 1\%).\textsuperscript{46–49,51–53} Despite the potential risk of these life-threatening complications, post-surgery prevention of thrombosis in LUL patients is not well established because risk stratification for this entity has not been achieved yet.

One of the hypotheses to explain the higher risk of thrombosis in this specific group is the existence of a longer pulmonary vein (PV) stump after LUL, which causes blood flow stasis resulting in the formation of the embolic source.\textsuperscript{46–47,55} In addition to altered flow in the vein stump, the postoperative blood flow changes in the LA are supposed to further promote the formation of thrombosis\textsuperscript{56–59} (Fig. 7).

\textbf{4D flow MRI evaluation of post-lung surgery}

For LA blood flow analysis in patients with LUL, a similar approach to AF has been performed. The Nippon Medical School group evaluated visual and quantitative analysis for this cohort using highly accurate 4D flow MRI with a dual-velocity encoding (VENC) scan. The regional and global blood flow significantly decreased compared to that in the healthy participants. In addition, they could visualize no flow directed to the junction between the LA and the stump of the LSPV\textsuperscript{57} (Fig. 8). Unexpectedly, the velocity parameters (mean velocity, maximum velocity, and stasis) did not differ between LUL patients with and without PVST.\textsuperscript{58} However, they clarified that the collision pattern was better maintained in patients without PVST compared to those with PVST (90\% vs. 37.5\%, \(P = 0.0188\)) (Figs. 9 and 10). This result may confirm the theory that physiological vortex flow is generated by the collision of the flow via the pulmonary vein.\textsuperscript{11,12} Another group evaluated the “turbulence” in the LA in patients after lobectomy.\textsuperscript{60} Care should be taken that some of the methodologies for the evaluation have not been confirmed except for their own study without any reference to healthy participants.\textsuperscript{61}

\textbf{Future Directions}

A technical challenging of 4D flow MRI acquisition in the LA is the limitation of the velocity noise ratio. In general, the main goal of LA analysis is to detect flow stasis (e.g., velocity \(< 10\, \text{cm/s}\)), so that the measurement accuracy for slow flow velocity is mandatory. However, VENC optimized for the heart (e.g., 100–200\, cm/sec) may not be suitable for this purpose. Currently, dual-VENC scans with a wider dynamic range of velocity have been attempted in LA analyses, although there is no concrete evidence that the significance of the improved velocity noise ratio overcomes the scan prolongation.\textsuperscript{57,58} Further investigation is required. The burden of segmentation hampers the clinical implementation of LA blood flow analysis. Deep learning-based segmentation has emerged in this field.\textsuperscript{62} Currently, computational flow dynamics in LA have been attempted using 4D CT data as the input.\textsuperscript{63–65} The combination of both methods can expand the flexibility of the analysis, such as shortening 4D flow MRI scan time, improving spatial resolution, and applying surgical-simulation.\textsuperscript{66}

\textbf{Conclusion}

There is still a debate on how blood flow can be defined in the disease conditions. Especially, in the LA, the fact that vortex flow already exists makes this debate more complicated. 4D flow MRI is expected to be able to capture non-physiological blood flow patterns from multiple aspects, such as blood flow velocity, stasis, and vortex quantification. This approach has been used to deal with diseases that are familiar to cardiologists (AF and after electrical conversion). Currently, the research target has widened to a disease familiar to lung surgeons (PVST after LUL). 4D flow MRI is expected to be utilized for many more diseases that are currently unimaginable.

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\textbf{Conflicts of Interest}

Makoto Obara is an employee of Philips Electronics Japan. Olgierd Leonowicz is a contractor of PMOD Technologies LIC. Only non-Philips or non-Pmod employee had edited this review paper. Except these authors, no conflicts of interest are declared.

\textbf{Supplementary Information}

A supplementary file below is available online.

\textbf{Supplemental Movie 1}

Flow in asymmetric and symmetric cavities after cessation of rocking. Momentum is conserved longer in the asymmetric model. This movie was reused from a published paper with the permission.\textsuperscript{11}

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