Prediction of Fontan-Associated Liver Disease Using a Novel Cine Magnetic Resonance Imaging “Vortex Flow Map” in the Right Atrium

Umiko Ishizaki, MD, PhD; Michinobu Nagao, MD, PhD; Yumi Shinya, MD, PhD; Kenji Fukushima, MD, PhD; Tatsunori Takahashi, MD, PhD; Yamato Shimomiya; Yuka Matsuo, MD, PhD; Kei Inai, MD, PhD; Shuji Sakai, MD, PhD

Background: Long-term hepatic dysfunction is an increasingly recognized complication of the Fontan operation for univentricular hearts. The purpose of this study was to determine whether Fontan-associated liver disease (FALD) could be predicted by flow dynamics in the right atrium (RA) of Fontan circulation.

Methods and Results: Cardiac MRI and the serum levels of total bilirubin (TBil) and hyaluronic acid (HA) were analyzed in 36 patients who underwent an atroipulmonary connection type of Fontan operation. The mean follow-up period was 53 months. Three views (axial, coronal, and sagittal) of the cine images were scanned for the maximum cross-section of the RA obtained with 1.5-Tesla scanner. We developed a “vortex flow map” to demonstrate the ratio of the circumferential voxel movement in each phase to the total movement throughout a cardiac cycle towards the center of the RA. The maximum ratio was used as the magnitude of vortex flow (MVF%) in the 3 views of the RA cine imaging. Patients with coronal MVF ≥13.6% had significantly lower free rates of TBil ≥1.8mg/dL than those with coronal MVF <13.6% (log-rank value=4.40; P<0.05; hazard ratio=4.12). Patients with sagittal MVF ≥14.0% had significantly lower free rates of HA ≥50ng/mL than those with coronal MVF <14.0% (log-rank value=4.40; P<0.05; hazard ratio=4.12).

Conclusions: A reduced vortex flow in the RA during the late phase of the Fontan operation was associated with the development of FALD. MVF can be used as an imaging biomarker to predict FALD.

Key Words: Cardiac magnetic resonance imaging; Fluid dynamics; Fontan procedure; Hyaluronic acid; Liver fibrosis

Since 1971, the Fontan procedure has been the standard treatment for patients with congenital heart disease (CHD) consisting of a single ventricle. Despite improved short-term survival, this palliative procedure is characterized by increased central venous pressure and has significant complications in the long term, including impaired ventricular function. The liver is one of the organs that suffer from the non-physiologic hemodynamics of the Fontan circulation. The increased inferior vena cava (IVC) pressure is transmitted directly to the bed of the liver because of the lack of valves in the hepatic veins. A significant body of evidence has shown that liver problems can be indicative of Fontan-associated liver disease (FALD), including liver cirrhosis and hepatocellular carcinoma. However, clinical markers of liver enzyme abnormalities, bilirubin levels, and even biopsies may not capture the extent of liver dysfunction and have not been correlated with clinical outcomes to date.

In asymptomatic patients with the atroipulmonary connection (APC) type of Fontan circulation, it is difficult to decide the optimal timing of a total cavopulmonary conversion (TCPC). The right atrium (RA) in a Fontan circulation gradually enlarges after the APC type of surgery. Patients with the APC type of Fontan circulation have significant backward flow in the IVC from the enlarged RA, leading to liver dysfunction. We hypothesized that RA flow dynamics in the APC type of Fontan circulation influence the development of FALD. The aim of the current study was to develop a novel imaging technique, also known as a vortex flow map (VFM), that can visualize and quantify vortex flow on conventional 2D cine magnetic resonance imaging (MRI) and to investigate how vortex flow in the Fontan circulation affects liver dysfunction. Furthermore, we investigated the predictive value of the vortex flow findings for FALD.

Received November 15, 2017; revised manuscript received March 25, 2018; accepted April 4, 2018; released online May 18, 2018

Time for primary review: 62 days

Department of Diagnostic Imaging & Nuclear Medicine (U.I., M.N., K.F., Y.M., S.S.), Division of Clinical Research for ACHD, Department of Pediatric Cardiology (Y. Shiina, K.I.), Department of Pediatric Cardiology (T.T., K.I.), Tokyo Women’s Medical University, Tokyo; Cardiovascular Center, St. Luke's International Hospital, Tokyo (Y. Shiina); and Clinical Application Development Marketing Division, Ziosoft Inc., Tokyo (Y. Shimomiya), Japan

Mailing address: Michinobu Nagao, MD, PhD, Department of Diagnostic Imaging and Nuclear Medicine, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: nagao.michinobu@twmu.ac.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@jcirc.or.jp
Methods

Patient Population
We retrospectively enrolled 36 consecutive adolescents and adult patients who had undergone the APC type of Fontan surgery (APC-Fontan) and subsequent cardiac MRI, standard laboratory testing, and contrast-enhanced abdominal computed tomography (CT) between April 2002 and December 2015. The surgeries included both classical and modified AP connection types of Fontan operation.12 There were no patients with implanted cardiac valve prostheses. For patients who had undergone the APC-Fontan procedure more than 10 years ago, a blood test examining liver function and fibrotic markers was performed at least every 6 months. Physicians determined the necessity for blood tests, ECG, chest radiography, echocardiography, and other examinations. FALD was defined as total bilirubin (TBil) level ≥1.8 mg/dL, hyaluronic acid (HA) level ≥50 ng/mL, or type 4 collagen 7S (collagen-7S) level ≥8.8 ng/mL during the follow-up period.13–17 The primary endpoint was the development of FALD (Figure 1A). The median collagen-7S value was 8.8 ng/mL for all patients with adult CHD, including a univentricular heart. In 36 patients, the mean TBil, HA, collagen-7S, and r-GTP levels at the time of cardiac MRI were 0.85 mg/dL, 25.7 ng/mL, 7.0 ng/mL and 73 IU/L, respectively.

For all 36 patients, abdominal contrast-enhanced CT was performed for an assessment of congestive liver disease and screening for hepatocellular carcinoma at least once during the study entry period. The mean CT attenuation for a circular region of interest (POI) with a diameter of

Table 1. Characteristics of 36 Patients With APC-Fontan

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Value (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at cardiac MRI</td>
<td>22±9.6</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>23/13</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153±13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46±14</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.39±0.26</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>DIRV/DILV</td>
<td>15 (42%)</td>
</tr>
<tr>
<td>AVSD</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>TA</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>DORV/TGA</td>
<td>13 (36%)</td>
</tr>
<tr>
<td>Age at Fontan completion (years)</td>
<td>4.7 (3.9–7.7)</td>
</tr>
<tr>
<td>Time to cardiac MRI since Fontan operation (years)</td>
<td>17.2±4.3</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>32 (89%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>106±16</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>66±18</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69±10</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>93±3.0</td>
</tr>
<tr>
<td>Laboratory examination</td>
<td></td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>87±37</td>
</tr>
</tbody>
</table>

AVSD, atrioventricular septal defect; DIRV/DILV, double-inlet right ventricle/double-inlet left ventricle; DORV/TGA, double-outlet right ventricle/ transposition of the great arteries; TA, tricuspid atresia.

Figure 1.  (A) Study protocol showing the duration between cardiac MRI after an atrio-pulmonary connection (APC)-Fontan operation, between cardiac MRI and abdominal CT and between cardiac MRI and liver function tests. Numeric data are expressed as mean± standard deviation (SD). (B) Representative case of a man in his 20s without Fontan-associated liver disease who underwent the APC-Fontan operation for double-outlet right ventricle and dextrocardia 17 years prior. Top row shows transaxial cine imaging throughout a cardiac cycle (Left, early-systole; Center, end-systole; Right, end-diastole), and Bottom row shows the vortex flow maps in the same phases. Cine imaging shows multiple dark flow phenomena in the dilated right atrium. The moving dark flow in the anterior portion (arrows) corresponds to a large vortex with hot colors. APC, atrio-pulmonary connection.
Vortex Flow Map in FALD

Vortex Flow Map in FALD

density-weighted spin-echo images in the transverse and angulated coronal planes in the orientation of the Fontan route for detailed anatomic depictions during breath-holds. Cine-balanced turbo field-echo sequences in the axial-view images and short-axis view images were acquired parallel to the atrioventricular groove from the base to the apex in patients with a single ventricle. The imaging parameters were: repetition time 2.8 ms, echo time 1.4 ms, flip angle 50°, slice thickness 8 mm, field of view 380 mm, matrix size 176×193, SENSE factor 2, 20 cardiac phases/RR intervals of the ECG. Cine MR images were analyzed semi-automatically, followed by manual correction using a workstation (Ziostation 2, Ziosoft, Tokyo, Japan). Volumes for the RA were measured on the axial images, as previously reported. End-diastolic and end-systolic phases were identified visually on those images that showed the largest and smallest RA cavity areas, respectively. The largest RA volume (mL) was used as a parameter because it might be associated with vortex flow formation or FALD.

3 cm in the right lobe of the liver was measured. Fatty degeneration was defined as parenchymal attenuation <50 Hounsfield units on non-contrast CT. Patients with abnormal parenchymal enhancement, hepatomegaly, and cirrhotic changes were evaluated by 2 radiologists, and patients with these findings were identified as positive for congestive liver disease. In addition, the presence of a hypervascular liver tumor was evaluated.

The study was approved by the institutional ethical review board and written informed consent was given by each subject. The indications for an initial Fontan surgery included various types of CHD described in Table 1. As a control group, 7 age-matched healthy controls (mean age, 25 years; males, 4) were also enrolled.

Cardiac MRI

All patients were examined while supine, using a 1.5-Tesla MRI scanner (Gyroscan ACS-NT, Philips Medical Systems, Best, The Netherlands) with a 4-element phased-array coil, with breath-holds during expiration and ECG gating. Localizing scans were followed by acquisition of proton density-weighted spin-echo images in the transverse and angulated coronal planes in the orientation of the Fontan route for detailed anatomic depictions during breath-holds. Cine-balanced turbo field-echo sequences in the axial-view images and short-axis view images were acquired parallel to the atrioventricular groove from the base to the apex in patients with a single ventricle. The imaging parameters were: repetition time 2.8 ms, echo time 1.4 ms, flip angle 50°, slice thickness 8 mm, field of view 380 mm, matrix size 176×193, SENSE factor 2, 20 cardiac phases/RR intervals of the ECG. Cine MR images were analyzed semi-automatically, followed by manual correction using a workstation (Ziostation 2, Ziosoft, Tokyo, Japan). Volumes for the RA were measured on the axial images, as previously reported. End-diastolic and end-systolic phases were identified visually on those images that showed the largest and smallest RA cavity areas, respectively. The largest RA volume (mL) was used as a parameter because it might be associated with vortex flow formation or FALD.
To obtain the VFM, the axial, sagittal, and coronal cine 2D images were scanned for the maximum cross-section of the RA. First, we delineated the contour of the RA for the ROI and determined the center of the long and short diameters of the RA on an initial cine image. Next, the VFM automatically tracked all pixels in the ROI and calculated the pixel movement for the ROI at each phase in relation to the total pixel movement throughout a cardiac cycle. The vector of pixel movement decomposes into circumferential and radial components. Movement in the circumferential direction is defined as vortex flow. The MVF is obtained from the equation:

$$\text{MVF} (%) = \frac{D(t) - D(0)}{D(0)},$$

where $D(t)$ is the moving distance at time $t$, and $D(0)$ is the distance at beggning. The maximum MVF was used as a representative value for a case. The great vortex flow was presented in hot colors and the small vortex flow or stagna-

**Vortex Flow Mapping**

Based on voxel and feature tracking methods, we modified the myocardial strain analysis for cine-tagging imaging of an existing software technique (Ziosation 2, Ziosoft)\(^2\,^23\) and developed the VFM, which enabled quantification and visualization of turbulent flow. The collision of fast and slow blood flow in the heart chamber generates turbulence, resulting in a non-uniform magnetic field. On conventional 2D cine imaging with steady-state free precession or balanced turbo field-echo sequences, a dark flow artifact is often seen in the enlarged Fontan circuit or normal RA (Figure 1B), which is caused by spins moving within an inhomogeneous magnetic field.\(^2\,^4\,^5\) In the dilated RA of an APC-Fontan, the turbulent flow is a mixture of pulsatile fast inflow from the IVC or superior vena cava (SVC) and stagnation in the chamber. Topics of VFM can specify attenuation by each voxel and automatically extract the voxel movement throughout the cardiac cycle.

Figure 3. A woman in her 40’s with Fontan-associated liver disease who underwent the APC-Fontan operation for double-outlet right ventricle 35 years prior. Her total bilirubin, r-GTP, hyaluronic acid, and collagen-7S levels at the last follow-up were 1.8 mg/dL, 120 mg/dL, 416 ng/mL and 13 ng/mL, respectively. (A) Vortex flow maps (VFM) show small flows in the transaxial (Left), coronal (Center), and sagittal (Right) views. Her transaxial, coronal, and sagittal magnitudes of vortex flow were 10.1%, 11.1%, and 12.9%, respectively. (B) Time curves of the magnitude of vortex flow for the 4 segments of the transaxial right atrium (RA) show 1 or 2 small peaks. The maximum (arrow) on the red line of the anterior segment was defined as the representative value of this case. Consequently, the magnitude of vortex flow was 10.1%. (C) Non-contrast CT shows a broad low-attenuation area in the liver, blurring of the hepatic shape, and swelling of the left lobe. Intrahepatic CT attenuation was 45 Hounsfield units (Left). Contrast-enhanced CT image shows diffuse and reticular abnormal enhancement areas in the whole liver, typical findings of congestive liver disease. APC, atriopulmonary connection.
tion was presented in cold colors (Figures 2,3).

**Statistical Analysis**
Continuous data are expressed as mean±standard deviation (SD). Comparisons of MVF and RA volume between patients with and without FALD were performed using the Mann-Whitney U-test. The correlation between MVF and other parameters was analyzed using Pearson’s correlation coefficient. A receiver-operating-characteristic (ROC) curve analysis was performed to determine the optimal cutoff of the MVF for the prediction of FALD. Survival curves of patient subgroups were created using the Kaplan-Meier method to clarify the time-dependent, cumulative FALD-risk. All statistical tests were 2-sided. A P value <0.05 was considered to indicate statistical significance. The analyses were performed using the JMP statistical program package (version 9.0; JMP, Inc., Cary, NC, USA).

**Results**

**Relevance of FALD**
The follow-up period for a blood test after cardiac MRI was 53±30 months (median, 52 months). There were 8 patients with TBil levels ≥1.8 mg/dL (22%), 11 patients with HA levels ≥50 mg/mL (31%), 15 patients with collagen-7S levels ≥8.8 ng/mL (47%), and 6 patients with r-GTP levels ≥120 IU/L (17%). The timing of the last abdominal CT after cardiac MRI was 40±26 months (median, 33 months); 12 patients with congestive liver disease (33%) and 7 patients with fatty liver disease (19%) were detected. Contrast-enhanced CT detected hypervascular liver tumors in 4 patients (13%). In one of the 4 patients, the tumor, which had a pattern of early enhancement and delayed washout, was diagnosed as a hepatocellular carcinoma. The other 3 cases without delayed washout were diagnosed as focal nodular hyperplasia. These nodular lesions had a diameter of less than 1.5 cm.

**Magnitude of Vortex Flow**
Transaxial, sagittal, and coronal MVFs for all patients who underwent APC-Fontan procedure were 21.2±12.4%, 17.5±9.9%, and 17.8±8.6%, respectively. Tranaxial and sagittal MVFs were significantly lower for patients who underwent APC-Fontan procedure than for controls (transaxial MVF, 44.8±29.1%, \( P<0.01 \); sagittal MVF, 38.6±13.7%, \( P<0.0005 \)). Coronal MVFs for controls could not be measured because the RA cavity was too narrow.

In patients who underwent the APC-Fontan procedure, MVF did not correlate with age or duration after Fontan operation (Pearson r=−0.22, P=0.33; Pearson r=−0.20, P=0.28). No correlation between MVF and the maximum RA volume was observed (Pearson r=−0.09, P=0.59).

On the transaxial VFM, vortex flow with an MVF ≥10.0% was seen in 50%, 40%, 40%, and 18% of the anterior, posterior, lateral, and medial regions of the RA, respectively, in the 36 patients. On the sagittal VFM, vortex flow with an MVF ≥10.0% was seen in 57%, 21%, 61%, and 4% of the 4 regions of the RA. On the coronal VFM, vortex flow with an MVF ≥10.0% was seen in 57%, 46%, 14%, and 14% of the 4 regions of the RA.

**Relationship Between MVF and FALD**
Transaxial MVF was significantly lower for patients with TBil levels ≥1.8 mg/dL than for those with levels <1.8 mg/dL. Coronal MVF was significantly lower for patients with elevations of TBil, HA, and collagen-7S levels than for those without. Sagittal MVF was significantly lower for patients with an elevation of HA than for those without. No significant difference in RA volume between patients with and without elevations of liver function markers was observed (Table 2).

Transaxial, coronal, and sagittal MVFs were significantly lower for patients with congestive liver disease than for those without. Transaxial MVF was significantly lower for patients with fatty liver disease than for those without. No significant difference in RA volume between patients with and without congestive liver or fatty liver disease was observed (Table 2).

**Prediction of Liver Disease Using MVF**
The ROC curve analysis revealed that the optimal coronal MVF was 13.6% for predicting patients with TBil level ≥1.8 mg/dL, with an area under the curve (AUC) of 0.92, 86% sensitivity and 86% specificity. The optimal sagittal MVF threshold was 14.0% for predicting patients with HA

---

**Table 2. Magnitude of Vortex Flow, RA Volume, and Fontan-Associated Liver Disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transaxial MVF (%)</th>
<th>P value</th>
<th>Coronal MVF (%)</th>
<th>P value</th>
<th>Sagittal MVF (%)</th>
<th>P value</th>
<th>RA volume (mL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type IV collagen 7S (ng/mL)</td>
<td>≥8.8</td>
<td>&lt;8.8</td>
<td>≥8.8</td>
<td>&lt;8.8</td>
<td>≥8.8</td>
<td>&lt;8.8</td>
<td>≥8.8</td>
<td>&lt;8.8</td>
</tr>
<tr>
<td>Hyaluronic acid (ng/mL)</td>
<td>≥50</td>
<td>&lt;50</td>
<td>≥50</td>
<td>&lt;50</td>
<td>≥50</td>
<td>&lt;50</td>
<td>≥50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>r-GTP (IU/L)</td>
<td>≥120</td>
<td>&lt;120</td>
<td>≥120</td>
<td>&lt;120</td>
<td>≥120</td>
<td>&lt;120</td>
<td>≥120</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>≥1.8</td>
<td>&lt;1.8</td>
<td>≥1.8</td>
<td>&lt;1.8</td>
<td>≥1.8</td>
<td>&lt;1.8</td>
<td>≥1.8</td>
<td>&lt;1.8</td>
</tr>
<tr>
<td>CT-congestive liver</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>CT attenuation (HU)</td>
<td>&lt;14.5</td>
<td>≥14.5</td>
<td>&lt;14.5</td>
<td>≥14.5</td>
<td>&lt;14.5</td>
<td>≥14.5</td>
<td>&lt;14.5</td>
<td>≥14.5</td>
</tr>
<tr>
<td>RA volume (mL)</td>
<td>14.8±10.8</td>
<td>12.6±10.8</td>
<td>16.0±10.8</td>
<td>20.5±10.8</td>
<td>10.5±10.8</td>
<td>24.7±10.8</td>
<td>10.5±10.8</td>
<td>24.7±10.8</td>
</tr>
</tbody>
</table>

All values are expressed as mean ± standard deviation. Comparison of RA volumes between patients with and without FALD was performed using the Mann-Whitney U-test.
level ≥50 ng/mL, with an AUC of 0.79, 80% sensitivity, and 74% specificity. The optimal coronal MVF threshold was 15.9% for predicting patients with a collagen-7S level ≥8.8 ng/mL, with an AUC of 0.78, 73% sensitivity, and 79% specificity.

Patients with coronal MVF ≥13.6% had significantly lower free rates of TBil levels ≥1.8 mg/dL than those with coronal MVF <13.6% (log-rank value=4.50, P<0.05) (Figure 4A). Patients with sagittal MVF ≥14.0% had significantly lower free rates of HA levels ≥50 ng/mL than those with sagittal MVF <14.0% (log-rank value=4.39, P<0.05) (Figure 4B). Patients with coronal MVF <15.9% had lower free rates of collagen-7S ≥8.8 ng/mL than those with coronal MVF ≥15.9% (log-rank value=3.47, P=0.06) (Figure 4C). The Cox hazard regression analysis showed that the hazard ratios were 4.54 for the development of TBil levels ≥1.8 mg/dL in patients with coronal MVF <13.6% and 4.11 for the development of HA levels ≥50 ng/mL in patients with sagittal MVF <14.0% (Table 3).

Discussion

The results of the current study suggested a new post-processing technique, VFM, to quantify and visualize vortex flow on conventional 2D cine MR imaging. VFM analysis revealed that decreased vortex flow in the RA was associated with development of FALD in the late phase after APC-Fontan operation, and that patients with high MVF have significantly lower free rates of FALD than those without it. MVF can be a good predictive marker for the development of FALD. Furthermore, we found significant correlation between small MVF and liver congestion on CT. In a representative case of a man in his 20s with hepatocellular carcinoma, the decreased coronal and sagittal MVF values were 9.8%, and 7.4%, respectively (Figure 5). There were 4 patients who showed elevations in TBil, HA, and collagen-7S levels; their average transaxial, coronal, and sagittal MVFs were 11.1%, 10.4%, and 12.5%, which were considerably decreased. Furthermore, there were 3 patients with hypoproteinemia and protein-losing enteropathy and 7 patients with jaundice: their mean coronary MVFs were 8.6% and 9.8%, respectively. Weak vortex flow is a sign of risk for liver cirrhosis, fibrosis, or hepatocellular carcinoma. The VFM provides important information on the management of liver complications during a long follow-up. The current study included 9 patients who underwent TCPC because of worsening heart failure and supraventricular arrhythmia: their average transaxial, coronal, and sagittal MVFs were 14.7%, 11.1%, and 12.6%, respectively. Lower MVF values could help in the decision-making process when considering TCPC because conversion should be performed just before major complications arise, even in asymptomatic patients.

MVF did not correlate with age or duration after APC-Fontan procedure. In contrast, the RA volume was not correlated with MVF or the development of FALD. MVF is an independent marker regardless of the time elapsed after a Fontan operation and is more reliable than the RA volume for predicting FALD. We speculate that the causes of a decreased MVF in the late phase after APC-Fontan procedure are: (1) gradually enlarging RA with subsequent poor contraction; (2) increased pulmonary vascular resistance because of passive blood flow through the lungs; and (3) flow energy loss caused by conflict in the SVC, IVC and Fontan route flows. In the early stage after AP connection

![Figure 4]
in caliber. Hence, blood stagnated in the RA. Large recirculating flows are observable in the APC-Fontan circulation, and colliding flow patterns are less observable compared with TCPC. \(^a\) Confluence of large, slow-speed recirculation flows and medium-speed tight vortices results in the turbulent flow in APC-Fontan, and is seen frequently at the ostium of the SVC. In contrast, the regions characterized by slow recirculation flow and stagnation are medial and inferior. This flow simulation corresponds to the distribution of vortex flow in our results. The coronal VFM was the most applicable view for detection of stagnation in the medial and inferior sites, which may be why the coronal MVF had the most significant association with the development of FALD.

Table 3. Cox Regression Analysis for Development of Fontan-Associated Liver Disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \chi^2 )</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin ( \geq 1.8 ) (mg/dL)</td>
<td>4.503</td>
<td>4.542</td>
<td>1.123–18.38</td>
<td>0.0338</td>
</tr>
<tr>
<td>Coronal MVF (&lt; 13.6% ) vs. ( \geq 13.6% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid ( \geq 50 ) (ng/mL)</td>
<td>4.399</td>
<td>4.115</td>
<td>1.097–15.43</td>
<td>0.036</td>
</tr>
<tr>
<td>Sagittal MVF (&lt; 14.0% ) vs. ( \geq 14.0% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IV collagen 7S domain ( \geq 8.8 ) (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronal MVF (&lt; 15.9% ) vs. ( \geq 15.9% )</td>
<td>3.47</td>
<td>2.685</td>
<td>0.9498–7.59</td>
<td>0.0625</td>
</tr>
</tbody>
</table>

MVF, magnitude of vortex flow.

Study Limitations

HA is the best-known biomarker of fibrosis in non-

surgery, RA contraction is preserved and there is turbulent flow in the large RA. By contrast, in the progressive and late stages, RA contraction is reduced and vortex flow disappears with the elevation in IVC pressure. \(^a\) Once the Fontan circulation deteriorates, blood flow becomes slow and stagnant. Recently, Shiina et al reported that weak vortex flow in the RA is a surrogate marker of supraventricular arrhythmia and thrombus after the APC-Fontan operation. \(^a\) Accordingly, vortex flow is considered to be the driving force maintaining Fontan circulation.

The coronal MVF was more significantly related to FALD than either the transaxial or sagittal MVF. High vortex flow is predominantly distributed in the superior and lateral sites of the RA, and is rarely seen in the inferior and medial sites. In a flow dynamics model of APC-Fontan circulation, velocity suddenly decreased once the blood entered the dilated RA from the IVC because of the change in caliber. Hence, blood stagnated in the RA. \(^a\) Large recirculating flows are observable in the APC-Fontan circulation, and colliding flow patterns are less observable compared with TCPC. \(^a\) Confluence of large, slow-speed recirculation flows and medium-speed tight vortices results in the turbulent flow in APC-Fontan, and is seen frequently at the ostium of the SVC. In contrast, the regions characterized by slow recirculation flow and stagnation are medial and inferior. This flow simulation corresponds to the distribution of vortex flow in our results. The coronal VFM was the most applicable view for detection of stagnation in the medial and inferior sites, which may be why the coronal MVF had the most significant association with the development of FALD.

Figure 5. A man in his 20s with hepatocellular carcinoma who underwent the APC-Fontan operation for double-outlet right ventricle 15 years prior. His total bilirubin, r-GTP, hyaluronic acid, and collagen-7S levels at the last follow-up were 1.0 mg/dL, 99 mg/dL, 169 ng/mL and 11.0 ng/mL, respectively. (A) Dynamic contrast-enhanced CT images shows a tumor with a diameter of 3 cm in the left lobe of the liver (arrow), which has a pattern of early enhancement and delayed washout (left upper, plain; right upper, arterial phase; left lower, portal phase; right lower, equilibrium phase). (B) Vortex flow maps (VFM) show small magnitude of vortex flows in the transaxial (Left), coronal (Center), and sagittal (Right) views. His transaxial, coronal, and sagittal MVFs were 16.5%, 9.8%, and 7.4%, respectively. APC, atrio pulmonary connection.
alcoholic fatty liver disease. The HA level in Fontan patients correlates with the change in portal vein hemodynamics, which might be an earlier indicator of liver fibrosis. However, Wu et al recently reported that the FibroSURE test and HA did not accurately predict the degree of histologic hepatic fibrosis. Although the relationship between elevation of HA and liver fibrosis is unclear in patients with Fontan circulation, our combined results for HA, collagen-7S, and abdominal CT suggested a strong relationship between decreased vortex flow in the RA and liver fibrosis.

A recent technique, 4-dimensional flow (4D-Flow) MRI, can visualize vortex flow and quantify wall shear stress and flow velocity. Suwa et al demonstrated the characteristics of intra-left atrial flow dynamics and factors affecting formation of vortex flow using this technique. However, a special sequence and software are required, and data acquisition and post-processing analysis are time-consuming and require specialized skills. Therefore, its clinical usage is still limited. The major advantage of VFM is that it does not require special sequences and can be applied retrospectively. Therefore, it is a simple, easy and user-friendly 2D technique that can be applied for the assessment of intra-ventricular flow. VFM analysis is expected to make clinical contributions. We hypothesize that the turbulence seen is a mixture between pulsatile fast inflow and stagnation. However, scientific definition of turbulence requires quantification of Reynolds number. Our MVFs were not verified with vorticity quantification in the analytic experiment. In addition, VFM quantifies the dark flow artifacts caused by spins moving within an inhomogeneous magnetic field. Therefore, the MVF may be influenced by the gradient magnetic field. The difference in MVD between 1.5- and 3-Tesla MRI scanners should be clarified. Furthermore, an alternative assessment to achieve information on liver disease at the time of cardiac MRI has been recently reported. Tagged MRI has been used for the assessment of liver stiffness and cardiac-induced liver deformation. The relationship between RA flow dynamics and liver stiffness in the Fontan circulation is a challenge for the future.

In conclusion, reduced vortex flow in the RA during the late phase of a Fontan operation was associated with the development of FALD. MVF can be used as an imaging biomarker to predict FALD.

Acknowledgment

This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (16K10321).

References

26. Bae JM, Jeon TY, Kim JS, Kim S, Hwang SM, Yoo SY et al. Late phase of a Fontan operation was associated with the development of FALD. MVF can be used as an imaging biomarker to predict FALD.


**Supplementary Files**

**Supplementary File 1**

**Figure S1.** Vortex flow maps of transaxial view for typical normal subjects show 1 or 2 peaks in mid-systole to mid-diastole in the fight atrium (RA).

**Supplementary File 2**

**Movie S1.** A woman in her 20s without Fontan-associated liver disease who underwent the APC-Fontan operation for double-outlet right ventricle 12 years ago. Her total bilirubin, r-GTP, hyaluronic acid, and collagen-7S levels at the last follow-up were 0.8 mg/dL, 61 mg/dL, 11 ng/mL, and 7.7 ng/mL, respectively. The vortex flow map (VFM) shows high magnitude of vortex flow as a hot color. The transaxial VFM shows colored vortex flows in the dominant anterior and posterior sites of the right atrium. A cold color shows small magnitude of vortex flow or stagnation.

Please find supplementary file(s):