Evaluation of takayasu arteritis with delayed contrast-enhanced MR imaging by a free-breathing 3D IR turbo FLASH

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Abstract
The primary aim of our case-control study was to observe delayed contrast-enhanced magnetic resonance imaging (DCE-MRI) in patients with Takayasu arteritis (TA) in comparison with magnetic resonance angiography (MRA). Twenty-seven patients including 15 with active TA and 12 with stable TA who underwent both aortic MRA and DCE-MRI were included. A total of 27 sex- and age-matched healthy volunteers were enrolled as the control group. MRA were obtained with T1WI-volume-interpolated breath-hold examination sequence or fast low-angle shot (FLASH) sequence. DCE-MRI was acquired with a free-breathing three-dimensional inversion recovery recovery Turbo fast low-angle shot (3D IR Turbo FLASH). Neither stenosis nor delayed enhancement of arterial wall was shown in the control group. In patients with stable TA, arterial stenosis was observed on MRA. On DCE-MR, delayed enhancement of arterial walls could be observed in the active TA group but not in the stable TA group or the control group. Stenotic arteries on MRA were comparable in the active TA and stable TA (χ²=2.70, P = .259); however, delayed enhancement of arterial walls in the active-TA group were more than those in the stable group (χ²=27.00, P < .001). Our results suggest that DCE-MRI with the free-breathing 3D IR Turbo FLASH sequence could assess TA and delayed enhancement on DCE-MRI is one characteristics of the active TA.

Abbreviations: CTA = computer tomographic angiography, 3D IR Turbo FLASH = three-dimensional inversion recovery turbo fast low-angle shot, RBC = red blood cell count, CRP = C-reactive protein, DCE-MRI = delayed contrast-enhanced magnetic resonance imaging, ESR = erythrocyte sedimentation rate, MRA = magnetic resonance angiography, NT-proBNP = N-terminal pro-brain natriuretic peptide, PA = pulmonary artery, RPA = right PA, TA = Takayasu arteritis, WBC = white blood cell count.

Keywords: delayed contrast-enhanced MR imaging, magnetic resonance angiography, Takayasu arteritis

1. Introduction
Takayasu arteritis (TA) is an idiopathic chronic inflammatory disease that primarily affects aorta, its major branches, and the pulmonary arteries. It is characterized by granulomatous inflammation of the arterial wall with marked intimal proliferation and fibrosis of the media and adventitia.[1] Early diagnosis and treatment of TA is important in preventing serious complications.

Conventional angiography, the criterion standard method for initial diagnosis, seems to be replaced with the imaging modalities such as computer tomographic angiography (CTA) or magnetic resonance imaging (MRI) in recent years.[2-4] CTA has been an important role in diagnosis and activity determination of TA[5]; however, radiation dose need to be considered. Contrast-enhanced 3-dimensional MR angiography (MRA) can noninvasively assess luminal stenosis or dilation without radiation; however, this method is limited to visualize situation of vessels wall. Delayed contrast-enhanced MR Imaging (DCE-MRI) has demonstrated its value for the detection of vessel wall alterations in TA.[6,7] Delay enhancement of arterial wall on DCE-MRI can be demonstrated with a delay after injection of gadolinium contrast material, which depicts progressive accumulation and delayed washout of contrast medium.

Recently, the free-breathing 3-dimensional inversion recovery turbo fast low-angle shot (3D IR Turbo FLASH) sequence[8,9] was developed to evaluate myocardial fibrosis in form of delayed enhancement in patients with cardiomypathy. Because inflammation and fibrosis[10] were pathological characteristics of arterial wall of TA, we hypothesized that delayed enhancement could be observed in TA by using a free-breathing navigator-gated 3D IR Turbo FLASH sequence. The purpose of this study is to observe DCE-MRI findings of TA with free-breathing 3D IR Turbo FLASH and compare DCE-MRI with MRA in patients with TA.

2. Methods

2.1. Participants
This is a case-control observational study. The institutional ethics committee of our hospital approved the study protocol and all participants gave the written informed consent for this study.

Observational Study
According to modified version of the Ishikawa diagnostic criteria for TA\textsuperscript{[11]} and the National Institute Health criteria,\textsuperscript{[12,13]} we prospectively included 15 patients with the actively TA from January 2016 to May 2017. Meanwhile, we screened 12 patients with the stable TA between January 2014 and October 2015 from medical charts. Twenty-seven sex- and age-matched healthy volunteers without a history of pulmonary, cardiovascular, or systemic diseases were enrolled as the control group. All participants underwent both aortic MRA and DCE-MRI. Demographic data were collected from all patients' medical charts.

### 2.2. Magnetic resonance imaging

All patients underwent MRI on 3.0-T scanner (Tim Trio, Erlangen, Siemens Healthcare, Germany) with a body-flex receiver coil. After scout imaging, MRA were obtained by using coronal and transversal T1WI-volume-interpolated breath-hold examination sequence (repetition time [TR]/echo time [TE]=3.20/1.23 ms, flip angle =10°, field of view (FOV)=400 x 400 mm, voxel size =1.8 x 1.3 x 2.5 mm, slice thickness =2 mm, slices per slab =60, slabs =1, matrix =320 x 224, bandwidth =560 Hz/pixel, generalized autocalibrating partially parallel acquisitions (GRAPPA) factor =2) or by using FLASH sequence (TR/TE=2.66/0.98 ms, flip angle =30°, FOV =500 x 500 mm, voxel size =1.3 x 1.0 x 2.5 mm, slice thickness =1.2 mm, slices per slab =88, slabs =1, matrix =512 x 256, bandwidth =650 Hz/pixel, GRAPPA factor =2) after injection of gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was applied at 0.2 mmol/kg body weight at a rate of 3 mL/s followed by a 20 to 30 mL normal saline flush from a separate syringe at a rate of 2 mL/s using a power injector (Mallinckrodt, St Louis). After 10 to 15 minutes, DCE-MRI was obtained with a free-breathing 3D IR Turbo FLASH sequence. A crossed pair navigator pulse was used for respiratory gating. This protocol was performed in a transversal slab covering ascending aorta, aortic arch and its branches, and thoracic descending aorta. Typical imaging parameters for 3D IR Turbo FLASH sequence were TR/TE=2.8/1.05 ms, flip angle =15°, TI=260 ms, bandwidth =610 Hz/pixel, number of k-space lines per cardiac cycle =35, data window duration =117 ms, FOV =340 x 280 mm, matrix =256 x 256, slices per slab =70, slabs =1, voxel size =1.3 x 1.3 x 3.0 mm, GRAPPA factor =2. The acceptable window of navigation was 2.5 mm, and respiratory motion adaptation was used.

### 2.3. Magnetic resonance images analysis

Two radiologists who were blinded to the clinical information independently reviewed MRA and DCE-MRI of each subjects, determined stenosis, and the delayed enhancement of arterial wall. Aorta with its main branches including branchiocephalic, subclavian artery, common carotid, ascending aorta, the aortic arch, descending thoracic aorta, abdominal aorta, and pulmonary artery (PA) were assessed. The luminal situation on MRA is classified into normal, stenosis/occlusion, and aneurismal dilatation. DCE-MRI of arterial wall was classified into the positive and negative delayed enhancement.

### 2.4. Statistical Analysis

Quantitative data were expressed as mean ± standard deviation and/or median value. Comparison of qualitative findings was performed by Chi-square test or Fisher exact test. Comparison of

| Case | Sex/age | Disease duration, mo | Disease activity | RBC | WBC | Platelet | Hemoglobin | ESR | CRP | NT-proBNP |
|------|---------|----------------------|-----------------|-----|-----|----------|------------|-----|-----|----------|
| 1 F22 | 1       | Active               | 3.8             | 8.22| 300 | 101      | 83         | 90.8| 90.13|          |
| 2 F30 | 4       | Active               | 5.55            | 7.21| 245 | 125      | 22         | 17.5| 103.2|          |
| 3 F30 | 3       | Active               | 3.91            | 15.82| 324 | 110      | 54         | 30.1| 33.53|          |
| 4 F38 | 24      | Active               | 4.64            | 6.76| 178 | 127      | 23         | 18.6| 394  |          |
| 5 F26 | 2       | Active               | 3.2             | 11.46| 553 | 77       | 118        | 186 | 45.12|          |
| 6 F26 | 1       | Active               | 4.05            | 10.79| 460 | 118      | 90         | 96.6| 156.71|          |
| 7 F30 | 2       | Active               | 4.68            | 5.9  | 303 | 148      | 21         | 22.1| 153.3|          |
| 8 F22 | 1       | Active               | 4.42            | 4.7  | 351 | 121      | 39         | 8.4 | 23.71|          |
| 9 F27 | 3       | Active               | 3.51            | 10.1 | 321 | 110      | 78         | 110 | 43.21|          |
| 10 F33| 4       | Active               | 4.71            | 7.96 | 266 | 102      | 27         | 23.9| 86.25|          |
| 11 F35| 5       | Active               | 4.77            | 10.12| 299 | 143      | 37         | 3.7 | 351.3|          |
| 12 F34| 2       | Active               | 4.03            | 3.98 | 389 | 119      | 25         | 21  | 58.81|          |
| 13 F27| 5       | Active               | 4.83            | 9.40 | 164 | 139      | 55         | 18.2| 37.51|          |
| 14 F28| 12      | Active               | 4.2             | 8.84 | 299 | 110      | 19         | 19.7| 54.45|          |
| 15 F32| 46      | Stable               | 3.9             | 7.37 | 288 | 105      | 22         | 12.5| 15   |          |
| 16 F30| 24      | Stable               | 4.53            | 8.39 | 340 | 119      | 2         | 3.6 | 1120|          |
| 17 F42| 60      | Stable               | 5.09            | 5.67 | 140 | 156      | 6          | 10.1| 1851|          |
| 18 F27| 24      | Stable               | 3.95            | 4.51 | 219 | 123      | 10         | 6.5 | 441.9|          |
| 19 F39| 12      | Stable               | 3.88            | 8.07 | 344 | 117      | 13         | 5.7 | 3641|          |
| 20 F43| 12      | Stable               | 3.83            | 7.9  | 335 | 126      | 16         | 6.1 | 551 |          |
| 21 F39| 48      | Stable               | 3.81            | 9.57 | 269 | 108      | 6          | 4   | 2995|          |
| 22 F42| 60      | Stable               | 4.24            | 6.98 | 143 | 140      | 2          | 7.4 | 4286|          |
| 23 M57| 36      | Stable               | 4.4             | 8.3  | 202 | 141      | 4          | 6.7 | 2397|          |
| 24 F42| 96      | Stable               | 4.67            | 3.71 | 142 | 113      | 3          | 1.1 | 210 |          |
| 25 F32| 24      | Stable               | 5.17            | 7.55 | 245 | 153      | 5          | 2.2 | 41.58|          |
| 26 F34| 24      | Stable               | 5.46            | 5.24 | 305 | 128      | 2          | 5.3 | 1795|          |
| 27 F42| 36      | Stable               | 4.01            | 6.93 | 253 | 132      | 4          | 2.5 | 1135|          |

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, RBC = red blood cell count, WBC = white blood cell count.
quantitative clinical and MRI findings was performed by Mann-Whitney U test. Analysis was performed with MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium). For all tests, a P value <.05 was considered statistically significant.

3. Results

3.1. Study participants

The clinical information of TA patients is shown in Table 1. TA patients included 1 man and 26 women, with median age of 34 years (range 22–43 years). Healthy control group included 1 man and 26 women with median age of 34 years (range 23–40 years). Sex and age (U = 335.00, P = .591) between TA and the healthy group are similar. Red blood cell count (RBC), white blood cell count (WBC), hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are shown in Table 2.

Table 2 shows the delayed enhancement of arterial wall in TA group. In the healthy group, no delayed enhancement of arterial wall was observed on DCE-MRI (Fig. 1). In the active group, DCE-MRI demonstrated the delayed enhancement of arterial wall (Fig. 2) including 3 cases in aorta and its branches, whereas the other 12 cases in both aorta and PA and their branches.

3.2. Magnetic resonance angiography and delayed contrast-enhanced magnetic resonance imaging

The stenotic arteries in the TA group are shown in Table 3. In the healthy group, none showed stenotic arteries on MRA (Fig. 1). In active TA group, MRA could show the stenotic arteries (Fig. 2). Five patients showed stenosis in aorta and its branches and 3 cases showed stenosis in PA and their branches, whereas 7 cases showed stenosis in both aorta and PA and their branches. There was no significantly difference of stenotic arteries between the active and stable TA patients (χ² = 2.70, P = .259).

Table 3 shows the delayed enhancement of arterial wall in TA group. In the healthy group, no delayed enhancement of arterial wall was observed on DCE-MRI (Fig. 1). In the active group, DCE-MRI demonstrated the delayed enhancement of arterial wall (Fig. 2) including 3 cases in aorta and its branches, whereas the other 12 cases in both aorta and PA and their branches.

Table 3

| Clinical and laboratory findings                  | Control group (n = 27) | TA (n = 27) | Active TA (n = 15) | Stable TA (n = 12) |
|--------------------------------------------------|------------------------|------------|-------------------|-------------------|
| Median age, yr                                   | 34 (22–40)             | 34 (22–43) | 30 (22–39)        | 39 (32–43)        |
| Sex (F/M)                                        | 23/4                   | 23/4       | 15/0              | 11/1              |
| RBC (× 10¹²/L)                                   | 4.65 ± 0.46            | 4.34 ± 0.59| 4.2*              | 4.32*             |
| WBC (× 10⁹/L)                                    | 6.52 ± 0.86            | 7.82 ± 2.59| 8.22*             | 7.27*             |
| Hemoglobin, g/L                                  | 143.78 ± 17.23         | 122.63 ± 17.88| 118               | 127               |
| Platelet (× 10¹²/L)                              | 232.03 ± 49.33         | 265.07 ± 94.09| 300*              | 249*              |
| ESR, mm/h                                        | 3.15*                  | 21*        | 31*               | 4.5               |
| CRP, mg/L                                        | 3.11*                  | 10.1*      | 21*               | 5.5               |
| NT-proBNP, pg/mL                                 | 19.68 ± 156.71*        | 58.81 ± 1465| 58.81             | 1465*             |

* Median value.

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, RBC = red blood cell count, TA = Takayasu arteritis, WBC = white blood cell count.
Furthermore, no delayed enhancement of arterial wall was observed in the stable TA group (Fig. 3). Delayed enhancement of arterial wall in the active TA group was more than the control group ($\chi^2 = 42.00, P < .001$) and the stable group ($\chi^2 = 27.00, P < .001$).

Arterial stenosis and delayed enhancement are documented in Table 4. On MRA, 32 and 43 stenotic arteries respectively were shown in the active and stable TA patients. The stenotic arteries in the stable TA group was more than those in the active TA group ($\chi^2 = 12.373, P = .031$). DCE-MRI demonstrated 81 arteries with delayed enhancement in the active TA group and none in the stable TA group. In comparison with the stable TA group, delayed enhancement of arterial walls are more in the active TA group ($\chi^2 = 27.00, P < .001$). Moreover, arteries with delayed enhancement are more than stenotic arteries in the active TA group ($Z = 3.745, P = .001$).

### 3.3. Pulmonary artery

On MRA, the stenotic PA was observed in 10 active and 7 stable TA patients. Stenotic PA were similar in the active and the stable group ($\chi^2 = 0.199, P = .656$). On DCE-MRI, delayed enhancement of PA was observed in 12 active TA cases. However, no delayed enhancement of PA was observed in the stable group. Compared with the stable TA group, delayed enhancement of PA were more in the active TA group (Fisher exact test, $P < .001$).
Table 4  

| MRI         | Active TA (n=15) | Stable TA (n=12) | P  |
|-------------|------------------|------------------|----|
| Arterial stenosis on MRA |                  |                  |    |
| BA          | 5                | 9                | .054|
| SA          | 10               | 11               | .182|
| CC          | 7                | 4                | .484|
| AA          | 0                | 0                | NA |
| Aah         | 0                | 1                | .444|
| ThAo        | 0                | 5                | .01 |
| AbAo        | 2                | 6                | .003|
| PA          | 10               | 7                | .706|
| Delay enhancement on DCE-MRI |                  |                  |    |
| BA          | 11               | 0                | <.001|
| SA          | 10               | 0                | <.001|
| CC          | 9                | 0                | <.001|
| AA          | 14               | 0                | <.001|
| Aah         | 15               | 0                | <.001|
| ThAo        | 8                | 0                | .003|
| AbAo        | 2                | 7                | .478|
| PA          | 12               | 0                | <.001|

AA = ascending aorta, Aah = aortic arch, AbAo = abdominal aorta, BA = brachiocephalic artery, CC = common carotid artery, MRA = magnetic resonance angiography, PA = pulmonary artery, SA = subclavian artery, TA = Takayasu arteritis, ThAo = thoracic descending aorta.

On MRA, 11 patients in the active group showed stenosis in right PA (RPA). On DCE-MRI, 2 patients showed the delayed enhancement of RPA, 5 patients showed delayed enhancement of MPA and RPA, and 5 patients showed delayed enhancement of MPA and bilateral PA. PA with delayed enhancement were more than the stenotic PA ($\chi^2 = 10.909$, $P = .012$).

4. Discussion

In this research, we demonstrated that delayed enhancement of arterial wall could be displayed by the free-breathing 3D IR Turbo FLASH sequence in patient with active TA, and delayed enhancement of arterial wall was the main finding of the active TA.

TA is a rare inflammatory disease mostly affecting young women. In our patients, 96.3% (26/27) patients with TA were women and there were no significantly difference of sex and age between the active and stable group. In comparison of the active group, the plasma CRP and ESR in the stable group decreased but significantly difference of sex and age.

Turbo FLASH sequence cannot be quantitatively measured, so it was reported that abnormal pulmonary angiography in patients with TA was about 30% to 74%. But Pulmonary artery involvement is often underestimated because pulmonary angiography is not a clinical routine examination. In our case, PA was affected in 52% cases (14/27). PA with delayed enhancement was more than the stenotic PA, suggesting the affected PA depicted DCE-MRI with 3D IR Turbo FLASH is more sensitive than MRA.

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