Myocardial Perfusion Imaging in Takayasu Arteritis

Cloé Comarmond, Odile Dessault, Jean-Yves Devaux, Nathalie Costedoat-Chalumeau, Matthieu Resche-Rigon, Richard Isnard, Fabien Koskas, Patrice Cacoub, and David Saadoun

ABSTRACT. ***Objective.*** Myocardial perfusion defects using scintigraphy have been frequently observed in patients with Takayasu arteritis (TA) without coronary stenosis. The aim of our study was to evaluate coronary microcirculation in TA using thallium-201 (201Tl) myocardial scintigraphy and dipyridamole (DPM) as vasodilator agent.

Methods. Twenty-five consecutive patients with TA were prospectively recruited. They were asymptomatic for cardiac issues and examined using 201Tl myocardial scintigraphy at rest and after coronary artery vasodilation with intravenous DPM. Factors associated with improvement in myocardial perfusion after DPM were identified in patients with TA.

Results. Among 25 patients with TA, 21 (84%) had 201Tl myocardial perfusion defects and 4 (16%) had normal resting myocardial perfusion. Using a 17-segments model for quantitative image analysis, DPM significantly improved resting 201Tl myocardial perfusion in 14 patients (61%) versus 9 patients without improvement (39%). We were able to examine coronary artery stenoses in 11 patients, including 10 patients with thallium perfusion defects, and significant coronary artery stenoses were present in only 2 patients (18.2%). No significant difference was found in traditional cardiovascular risk factors between TA patients with or without improvement of myocardial perfusion after DPM. The absence of improvement in myocardial perfusion after DPM tended to be closely associated with specific features and prognostic factors of TA, such as aortic regurgitation at diagnosis, renovascular hypertension, longer duration of TA disease, and male sex.

Conclusion. We found the significantly high prevalence of myocardial perfusion defects mostly improved after vasodilation with DPM, which may indicate the major role of microcirculatory dysfunction in myocardial ischemia in TA. (J Rheumatol First Release Oct 15 2013; doi:10.3899/jrheum.130308)

Key Indexing Terms:
TAKAYASU ARTERITIS VASCULITIS MYOCARDIAL ISCHEMIA
MICROCIRCULATION SCINTIGRAPHY

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Takayasu arteritis (TA) is a chronic inflammatory vasculitis of unknown origin affecting large vessels, predominantly the aorta and its main branches. This large vessel vasculitis leads to multiple organ damage caused by vessel inflammation and chronic ischemia. Although once thought to be a disorder that mostly affected young Asian women, TA has been identified in both sexes of many ethnic and racial groups worldwide[1].

Myocardial involvement in TA is considered a major cause of morbidity and mortality. Myocardial ischemia is rarely clinically evident and coronary arteries are involved in < 10% of patients with TA[1,2,3,4]. However, myocardial perfusion defects using myocardial scintigraphy and myocardial scarring on cardiac magnetic resonance imaging (MRI) have been observed in 53% to 78% and 27%, respectively, of asymptomatic patients with TA[5,6,7]. The mechanisms of myocardial ischemia in patients with TA remain unclear. Several cases of myocarditis with biopsy have proven small myocardial vessel involvement[8,9]. Considering the high frequency of silent myocardial ischemia in patients with TA and without epicardial

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coronary stenosis, the potential role of coronary microcirculation should be analyzed.

The aim of our study was to evaluate coronary microvascular dysfunction in TA using thallium-201 (201Tl) myocardial scintigraphy and dipyridamole (DPM) as the vasodilator agent.

MATERIALS AND METHODS

Patients. Twenty-five consecutive patients with TA were prospectively recruited from our Department of Internal Medicine (Groupe Hospitalier Pitié-Salpêtrière, Paris, France) between December 2010 and January 2012. All patients met ≥ 3 of the 1990 American College of Rheumatology classification criteria for TA[10]. Potential confounding conditions (giant cell arteritis, Cogan syndrome, Behçet disease, Kawasaki disease, syphilis, tuberculosis aortitis, vascular Ehlers-Danlos syndrome, Marfan syndrome, and neurofibromatosis) were excluded. Diagnosis of TA was based on clinical, biological, and imaging data (i.e., vascular echography, arteriography, angio-computed tomography, and/or magnetic resonance angiography). We classified patients into 6 types according to the Numano classification[11]. Disease activity of patients with TA was defined according to the National Institutes of Health criteria defined by Kerr, *et al*[1]. For each patient, the following data were recorded at the time of 201Tl myocardial scintigraphy: age at onset of TA symptoms, sex, geographic origin, cardiovascular risk factors [i.e., smoking, hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg)], hypercholesterolemia (low-density lipoprotein cholesterol > 130 mg/dl), overweight (body mass index > 25 kg/m^2), diabetes, clinical features of TA (systemic and/or vascular symptoms), current treatment, and laboratory data [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), troponin, creatinine]. The cutoff titers used to define abnormal CRP and ESR were > 4 mg/l and > 15 mm/h, respectively. Physical examination, electrocardiography (EKG), and transthoracic echocardiography were performed. All patients provided their informed consent to participate.

EKG and transthoracic echocardiography measurements. A standard resting 12-lead EKG was recorded and analyzed by an experienced physician. Echocardiographic examinations were performed in standard parasternal, apical, and subxiphoidal views. The left ventricle ejection fraction (LVEF) was calculated in a standard manner and was used to assess global LV systolic function. Abnormalities were reported as wall motion abnormalities, myocardial hypertrophy, and valvular regurgitation.

DPM 201Tl myocardial scintigraphy. Scintigraphic imaging was performed using SYMBIA S or T2 (Siemens Medical), composed of a dual-head variable-angle gamma camera and a 2-slice computed tomographic (CT) scanner (32 projections were acquired over a 180° orbit into a 64 × 64 matrix, and a time per projection of 45 s). Day 1: 201Tl myocardial single photon emission-CT (SPECT) scintigraphy was performed 15 min after thallium chloride injection (75 to 150 MBq). Day 7: pharmacologic vasodilator effect was induced with administration of DPM in all patients, except 2 patients with contraindications. Scintigraphic imaging started 10 min after the end of the DPM infusion (0.56 mg/kg body weight) and the injection of thallium chloride (75 to 150 MBq)[6,7,12]. Tomographic images were reconstructed after filtered back projection with a Butterworth filter. Myocardial ischemia caused by coronary artery disease (CAD) is commonly assessed using 201Tl imaging with DPM stress as an alternative to dynamic exercise[13,14]. Usually, DPM is used as a pharmacologic stress agent to induce perfusion defects in myocardial territories with large coronary artery stenoses through a coronary steal mechanism. Hypoperfused segments after DPM have normal or improved perfusion at rest, and nonperfused segments (myocardial scarring) show no change between DPM and rest. If the myocardial defect observed after DPM is corrected at rest, there is a significant stenosis causing reversible ischemia. If the myocardial defect observed after DPM is not corrected at rest, it corresponds to a typical myocardial infarction (myocardial scarring). Here, conversely, we used DPM as a vasodilator to produce improvement of resting thallium defects in myocardial territories with coronary microvascular dysfunction. This reverse effect is observed when DPM improves resting thallium perfusion, due to vasodilator activity of DPM on small coronary arteries[15,16]. Thus, macrovascular and microvascular dysfunctions can be distinguished using DPM 201Tl myocardial scintigraphy. The protocol of myocardial SPECT performed in our present study (resting and DPM 201Tl imaging performed at 1-week intervals) was identical to those used in studies supporting the benefit of vasodilator drugs for improvement in 201Tl myocardial perfusion in patients with systemic sclerosis (SSc)[17,18].

Quantitative image analysis. Image analysis was performed by consensus of 2 nuclear diagnosticians who were blinded to the patient history. However, they were aware that the patients had TA. The 17-segments model[19,20] was used to analyze myocardial perfusion, and each segment was graded using a 5-point scoring system (0 normal perfusion, 1 mild hypoperfusion, 2 moderate hypoperfusion, 3 severe hypoperfusion, and 4 absence of photon activity). In each patient, scintigraphic image myocardial perfusion scores (summed rest score, summed stress score, and summed difference score) were determined. In our study, myocardial microcirculation impairment was diagnosed when DPM significantly improved myocardial perfusion (summed difference score ≥ 3). Microcirculation myocardial impairment was classified in 4 degrees of probability. Strong probability (degree 3) was defined when total score was improved after DPM with a summed difference score ≥ 5, intermediate probability (degree 2) when the number of segments improved after DPM was ≥ 3, low probability (degree 1) when the number of segments improved after DPM was equal to 1 or 2, and null probability (degree 0) in the absence of improvement after DPM.

Coronary CT angiography. CT data were acquired using a 64-slice CT scanner (Siemens Healthcare). Scan measurements were set as follows: collimation 2 × 32 × 0.6 mm, gantry rotation time 330 ms, tube current 700 mA with electrocardiography-based tube current modulation, and tube voltage 100 to 120 kV. The scan length extended from the carina to the diaphragmatic crura. The entire heart was scanned during a single breath-hold. First a noncontrast scan was performed for calcium score. The coronary arteries were visualized without contrast medium and 30 to 40 consecutive images were obtained at 3-mm intervals. The total coronary artery calcium score was determined by summing individual lesion scores from each of 4 anatomic sites. Then, scan delay after contrast injection was determined using a test bolus technique with 20 ml of nonionic iodated contrast material (iopamidol 370 mg I/ml; Bayer Schering Pharma AG). For coronary CT angiography, 90 ml of contrast material was administered at a rate of 5 ml/s. None of the patients showed adverse reactions to the contrast medium or complications during or after the study. Coronary arteries were analyzed according to a 17-segment model, and detectable coronary artery lesions were classified as (1) nonsignificant (< 50% luminal diameter reduction); (2) significant (≥ 50% luminal diameter reduction); or (3) occlusion. In addition, coronary artery lesions were classified as noncalcified, partly calcified, or completely calcified. According to prior definition, ostial lesions were defined as any plaque within 3 mm of the takeoff of the coronary artery from the aorta[21]. Patients with coronary lesions on CT coronary angiography were referred to catheterization.

Invasive coronary angiography. Cardiac catheterization was performed in 11 patients using standard techniques, all for preoperative risk evaluation before vascular surgery. An experienced interventional cardiologist analyzed the severity of visually detected stenoses.

Statistical analysis. Data are expressed as median [interquartile range (IQR)] for quantitative variables or counts and percentage for categorical variables. Comparisons between quantitative variables were performed using a nonparametric paired Wilcoxon test and Fisher's exact test for categorical variables. P values < 0.05 were considered significant. Tests were performed using computer software (SPSS Statistics, version 17.0; SPSS Inc.).

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RESULTS

Patient data. Twenty-five consecutive patients with TA were studied, with a predominance of females (72%). Their median age at the time of enrollment was 48 years (32.5–60.5). Patients had TA for a median duration of 9 years (4.5–14). Patients were white (68%), African (14%), North African (10%), Asian (6%), and Indian (2%). Cardiovascular risk factors included arterial hypertension (n = 9), dyslipidemia (n = 8), overweight (n = 9), family history of coronary arterial disease (n = 3), tobacco use (n = 6), and diabetes (n = 3). Twenty-three patients (92%) received corticosteroids. Immunosuppressive drugs were prescribed in 19 patients (76%). In addition, patients received low-dose aspirin [n = 18 (72%)], clopidogrel [n = 7 (28%)], anticoagulant [n = 3 (16%)], antihypertensive drugs [n = 8 (32%)], and statins [n = 22 (88%)].

Myocardial damage assessment by visual and quantitative analysis. Myocardial involvement was assessed using 201Tl myocardial scintigraphy at rest and upon DPM vasodilation. Scintigraphic myocardial perfusion defect due to microcirculation impairment is characterized by the reversibility of the defect using DPM. Myocardial perfusion defects at rest have been detected in 21 patients (84%) using 201Tl myocardial perfusion imaging. Using a 17-segments model for quantitative image analysis, DPM significantly improved resting 201Tl myocardial perfusion in 14 patients (61%) (reversible defects in at least 3 segments) versus 9 patients (39%; permanent defects or reversible defects in < 3 segments). Two patients presented contraindication to DPM test. Microcirculatory myocardial impairment was detected in 8 patients (35%) with strong probability, 6 (26%) with intermediate probability, in 6 (26%) with low probability, and 3 (13%) with null probability. Figures 1 and 2 illustrate the findings in a representative patient with strong probability of coronary microvascular impairment. Arrows show severe defects of myocardial perfusion observed at rest (A), and significantly improved upon DPM vasodilation (B).

Coronary angiography and CT. We were able to examine epicardial coronary lesions in 11 patients, including 10 patients with thallium perfusion defects at rest. Among patients with thallium perfusion defects, significant coronary artery stenoses were present in only 2 patients (18%). Large coronary artery involvement in these 2 patients was also detected with stress DPM thallium scintigraphy. In 1 patient, coronary angiography revealed 70% stenosis of interventricular anterior artery treated by coronary artery bypass grafting. DPM induced or worsened myocardial perfusion defects in 6 segments (segments 1, 3, 4, 13, 15, and 17); it improved perfusion in only 1 (segment 2), with a low probability of myocardial microcirculation

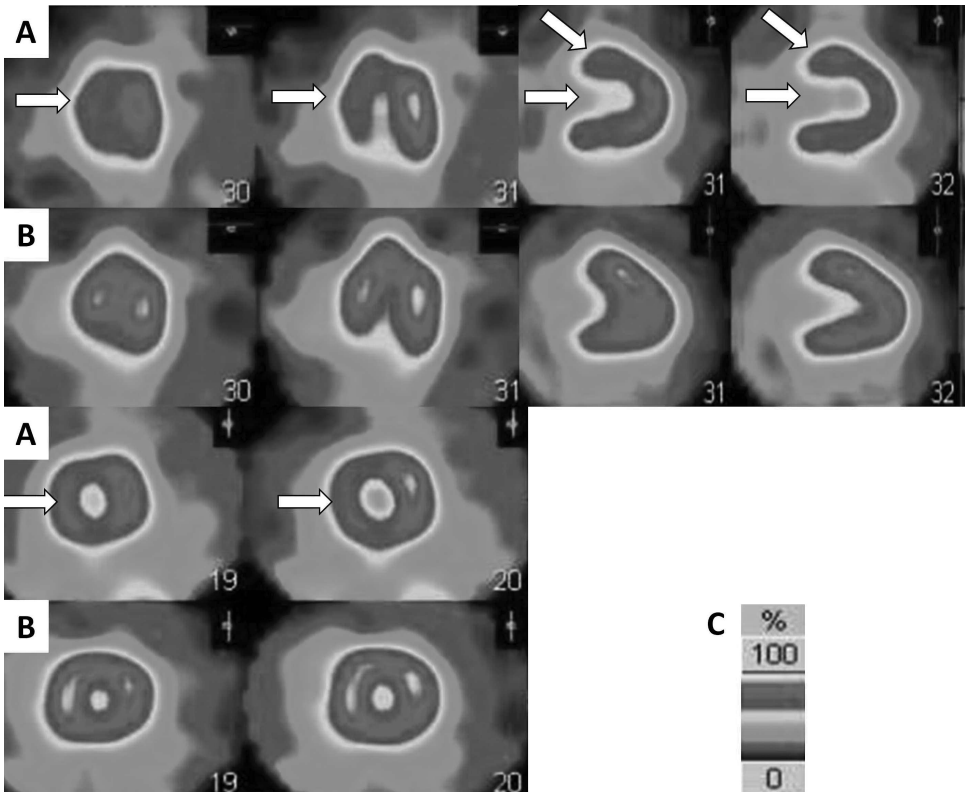

Figure 1. Thallium single photon emission-computed tomography images showing myocardial perfusion defect (white arrows) improved upon dipyridamole (DPM) in a 45-year-old patient with Takayasu arteritis. The images were obtained at rest (A) and after DPM (B). The percentage of perfusion defect is represented by the scale (C).

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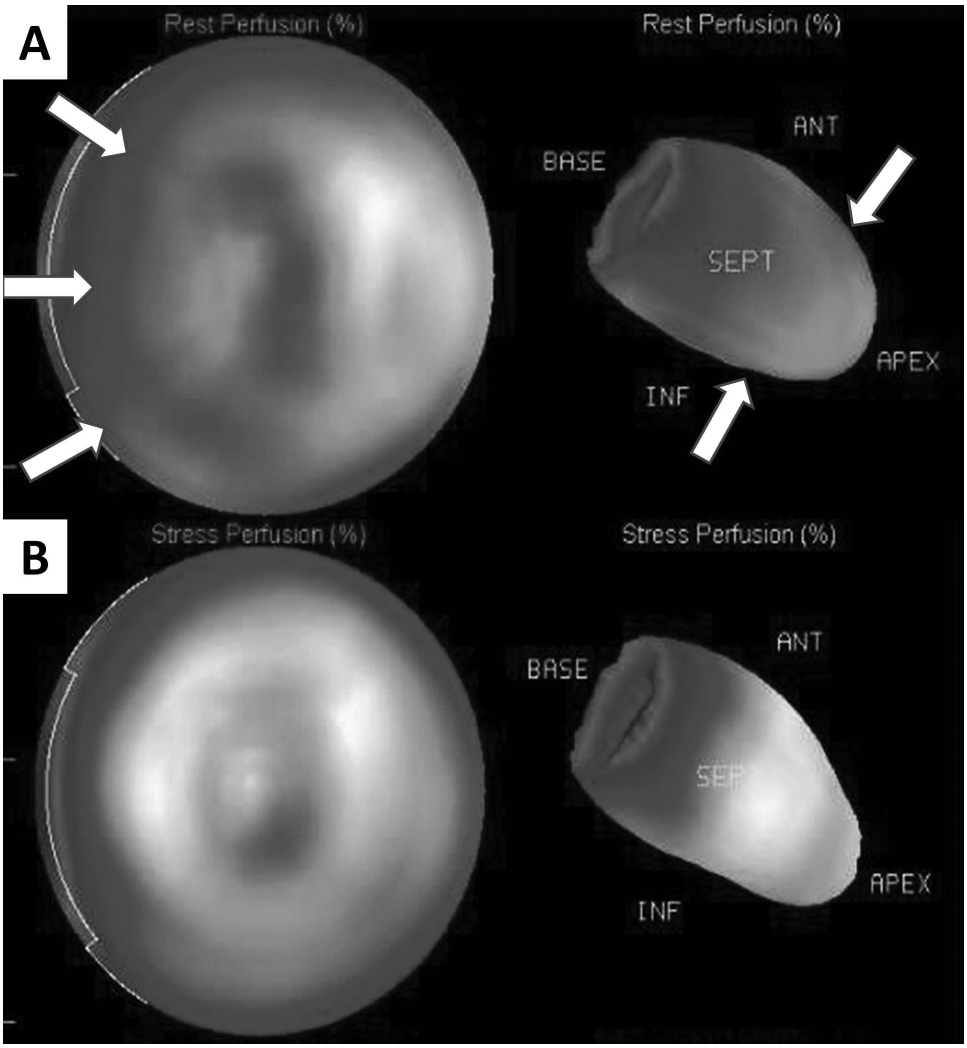

Figure 2. Polar slices obtained from the same patient as in Figure 1. There are severe defects (white arrows) in the anterior (ANT), inferior (INF), and septal (SEPT) segments at rest (A) that partially reverse during coronary artery vasodilation with dipyridamole (B).

impairment. The second patient presented a severe marginal stenosis treated by angioplasty and placement of a stent. DPM induced or worsened myocardial perfusion defect in 5 segments (5, 6, 11, 12, and 16), and improved myocardial perfusion in 7 segments (1, 2, 3, 7, 8, 9, and 14) with an intermediate probability of myocardial microcirculation impairment, illustrating that both types of vascular dysfunction may occur in the same patient.

Biologic, EKG, and echocardiography findings in patients with TA. Data are summarized in Table 1. Except for 1 patient with TA dialyzed for chronic kidney disease, levels of serum creatinine [median 76.5 (69-87) μmol/l)] were all within the normal range. No difference was observed according to levels of CRP or ESR between patients with and without DPM improvement. No patients with TA had Q waves on EKG findings. Three patients with TA presented a right bundle branch block with no statistical difference between the 2 groups. Echocardiography showed thickening of the mitral or aortic valves in 10 patients with TA, moderate septal or left ventricle hypertrophy in 4 patients, and segmental wall motion abnormalities in 4 patients, with no statistically significant difference between the 2 groups. All patients had left ventricle ejection function (LVEF) within normal ranges [median 58% (55% to 62%)]. Five (55.6%) of 9 patients without myocardial perfusion improved after DPM and 6 (42.9%) of 14 patients with DPM improvement had normal findings on echocardiography ($p = 0.834$).

Factors associated with myocardial perfusion improvement after DPM were identified in patients with TA. The clinical characteristics of the patients with TA and presence or absence of myocardial perfusion improvement after DPM are shown in Table 1. We found no statistically significant difference in age, sex ratio, race, and frequency of tradi-

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Table 1. Comparison of baseline characteristics and cardiovascular risk factors between Takayasu arteritis (TA) patients with improvement or without improvement in myocardial perfusion after dipyridamole ($p < 0.05$).

Characteristics	All Patients, n = 25	No DPM Improvement, n = 9	DPM Improvement, n = 14	p
Age, yrs (range)	48 (32.5–60.5)	56 (43–60)	46.5 (28–63.5)	0.738
Women (%)	18 (72)	5 (55.6)	12 (85.7)	0.171
White (%)	17 (68)	6 (66.7)	10 (71.4)	1.000
Age at onset of disease symptoms, yrs (range)	36 (25.5–49)	36 (27–46.5)	38.5 (24.5–53)	0.205
Disease duration, yrs (range)	9 (4.5–14)	10 (6–22.5)	6 (2.75–10.75)	0.878
Angiographic classification of TA, Numano type				0.277
I	6 (24)	3 (33.3)	3 (21.4)	
IIa	1 (4)	1 (11.1)	0	
IIb	2 (8)	0	1 (7.1)	
III	5 (20)	3 (33.3)	2 (14.3)	
IV	0	0	0	
V	11 (44)	2 (22.2)	8 (57.1)	
Ishikawa clinical classification				0.686
1	9 (36)	3 (33.3)	5 (35.7)	
2	11 (44)	4 (44.4)	7 (50)	
3	5 (20)	2 (22.2)	2 (14.3)	
Major complication at diagnosis (%)				
Aortic regurgitation	5 (20)	4 (44.4)	0	0.009
Aneurysm	8 (32)	3 (33.3)	5 (35.7)	1.000
Retinopathy	3 (12)	0	2 (14.3)	0.157
Disease activity, NIH (%)				0.937
0	12 (48)	5 (55.6)	6 (42.9)	
1	3 (12)	1 (11.1)	2 (14.3)	
2	6 (24)	2 (22.2)	4 (28.6)	
3	4 (16)	1 (11.1)	2 (14.3)	
No. of arterial territories involved (range)	5 (3–7)	5 (2–8)	6 (3–8)	0.781
BMI, kg/m^2 (range)	24.9 (22.8–28.8)	24.7 (23.8–28.4)	24.75 (22–28)	0.675
Heart pulsation (range)	74 (67–82.5)	73 (66.5–82.5)	75 (66–86)	1.000
Systolic blood pressure, mm Hg (range)	130 (119-143)	139 (125.5–147.5)	125 (114–138)	0.941
Diastolic blood pressure, mm Hg (range)	74 (68–80)	78 (69–79)	75 (67–80)	0.663
Electrocardiographic findings (%)				
Normal	22 (88)	6 (66.7)	14 (100)	0.078
Conduction block	3 (12)	3 (33.3)	0	
Q waves	0	0	0	
Renovascular hypertension (%)	9 (36)	5 (55.6)	4 (28.6)	0.359
History of dyslipidemia (%)	8 (32)	3 (33.3)	5 (35.7)	1.000
History of diabetes (%)	3 (12)	2 (22.2)	1 (7.1)	0.644
Family history of CAD (%)	3 (12)	1 (11.1)	2 (14.3)	1.000
Tobacco use (%)	6 (24)	3 (33.3)	3 (21.4)	0.797
Medications at enrollment				
Current corticosteroids (%)	23 (92)	8 (88.9)	13 (92.9)	1.000
Corticosteroids, mg/day (range)	15 (9–20)	10 (5–30)	15 (10–20)	0.314
Current immunosuppressive agents	19 (76)	7 (77.8)	10 (71.4)	1.000
Methotrexate	18 (72)	6 (66.7)	10 (71.4)	1.000
Mycophenolate mofetil	1 (4)	1 (11.1)	0	0.440
Anti-TNF	3 (12)	0	2 (14.3)	0.157
Aspirin	18 (72)	6 (66.7)	11 (78.6)	0.525
Clopidogrel	7 (28)	2 (22.2)	5 (35.7)	0.825
Statins	22 (88)	9 (100)	12 (85.7)	0.157
Antihypertensive agents	8 (32)	5 (55.6)	3 (21.4)	0.204
Anticoagulation	3 (12)	2 (22.22)	1 (7.1)	0.644
Laboratory measurements				
CRP, median (IQR), mg/l (range)	8 (4–11.5)	4 (3–23)	9.5 (3–11)	0.167
Abnormal CRP level, > 4 mg/l (%)	8 (32)	2 (22.2)	4 (28.6)	0.162
ESR, median (IQR) mm/h (range)	14 (10–30)	21.5 (5–42.5)	12.5 (8–19)	0.707
Abnormal ESR level, > 15 mm/h (%)	9 (39.1)	5 (62.5)	3 (23.1)	0.155
Creatinemia, median (IQR) μmol/l (range)	76.5 (69–87)	79 (67–101)	75 (67–80)	0.286
Cholesterol, median (IQR) g/l (range)	1.7 (1.52–2.6)	1.8 (1.55–2.65)	1.69 (1.48–2.61)	1.000
Troponine	All negative	All negative	All negative	NA
Echocardiographic findings				
Normal (%)	12 (48)	5 (55.6)	6 (42.9)	0.834
Segmental wall motion abnormalities (%)	4 (16)	1 (11.1)	2 (14.3)	0.482
Septal and/or left ventricle hypertrophy (%)	4 (16)	1 (11.1)	2 (14.3)	0.482
Mitral and/or aortic valvulopathy (%)	10 (40)	4 (44.4)	5 (35.7)	1.000
LVEF, % (range)	58 (55–62)	57 (53–61)	59 (55–63)	0.562

BMI: body mass index; NIH: National Institutes of Health; CAD: coronary artery disease; TNF: tumor necrosis factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DPM: dipyridamole; LVEF: left ventricle ejection fraction; NA: not applicable; IQR: interquartile range.

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tional coronary risk factors, including current blood pressure, diabetes, hypercholesterolemia, smoking, family history of CAD, and body mass index between the 2 groups.

Aortic regurgitation was associated with the absence of improvement in myocardial perfusion after DPM, occurring in 44.4% versus 0% in no DPM improvement and DPM improvement groups, respectively (p = 0.009). Patients without DPM improvement tended to have a longer duration of TA disease compared with those with DPM improvement [median (IQR) age 10 (6–22.5) yrs vs 6 (2.75–10.75) yrs], but the difference was not statistically significant (p = 0.878). Median age at onset of TA disease symptoms was similar in the 2 groups: 36 (27–46.5) years in group without DPM improvement versus 38.5 (24.5–53) in group with DPM improvement (p = 0.741). The presence of renovascular hypertension and male sex tended to be more frequent in TA patients without DPM improvement than in TA patients with DPM improvement [55.6 vs 28.6% (p = 0.359) and 44.4 vs 14.3% (p = 0.171), respectively]. Disease activity did not differ between the 2 groups. Improvement in myocardial perfusion after DPM was not associated with the use of medications such as prednisone (p = 0.314), immunosuppressants (p = 1.000), aspirin (p = 0.525), clopidogrel (p = 0.825), statins (p = 0.157), oral anticoagulant (p = 0.644), or antihypertensive agent (p = 0.204).

DISCUSSION

To our knowledge, our findings are the first to demonstrate that myocardial involvement in TA is mainly related to microcirculation impairment. We found a significantly higher frequency of resting myocardial perfusion defects in up to 80% of patients with TA, without clinical evidence of myocardial ischemia. Moreover, DPM significantly improved 201Tl myocardial perfusion in 61% of patients with TA. These results are quite different from those observed in patients with CAD, in which defects are unchanged or enhanced after intravenous DPM. Our study showed partial or total regression of myocardial perfusion defects at rest in patients with TA after DPM administration, making the presence of stenosis in epicardial coronary arteries unlikely. These data are confirmed by the low frequency of coronary stenosis (18%) observed in our patients with myocardial perfusion defects and consistent with previous studies in which epicardial coronary lesions are rare (< 10%) in patients with TA using coronary arteriography and postmortem examination.

In large TA cohorts with longterm outcome, cardiac involvement in TA is one of the most important causes of morbidity and mortality, but cardiac manifestations are reported in only 17% of patients with TA[1,2,3,4]. Deaths are due to congestive heart failure in 7% to 35% of cases, and acute myocardial infarction in 14% of cases[2,3]. Several earlier studies have been conducted on myocardial involvement in TA by using exercise 201Tl myocardial scintigraphy, but they never used DPM as a vasodilator[6,7,12]. Despite abnormal 201Tl, myocardial perfusion was reported in 53% to 78% of patients with TA; only 9% of patients with TA had epicardial coronary artery lesions[3,6,7]. To our knowledge, our study is the first to consider that abnormal myocardial perfusion in TA may be due in part to disturbance of the coronary microcirculation. Moreover, factors associated with myocardial perfusion defects have not been previously analyzed and identified in patients with TA. The absence of myocardial perfusion improvement after DPM in TA was significantly more frequently associated with aortic regurgitation at diagnosis, which is considered a poor prognosis factor[2]. We were not able to demonstrate a statistically significant association between other features of TA and myocardial perfusion improvement after DPM. However, renovascular hypertension, longer duration of TA disease, and male sex tended to be associated with the absence of myocardial perfusion improvement after DPM in TA. Further studies with larger numbers of patients with TA are warranted to determine whether the detection of myocardial perfusion defects not improved after DPM is a predictor of major cardiac events and death related to the heart in TA.

We performed 201Tl myocardial scintigraphy at rest and after DPM to investigate the short-term vasodilator effect of DPM on myocardial perfusion in patients with TA. This scintigraphic technique has been previously used to detect myocardial perfusion defects in sarcoidosis[22,23] and in SSc[17,18]. DPM significantly improved resting 201Tl myocardial perfusion in 13/19 patients (81%) with sarcoidosis and 12/23 patients (52.2%) with SSc[17]. Currently, it is not possible to obtain a control group because this scintigraphic technique is not performed on patients with noninflammatory diseases or routinely for chest pain. We chose to use 201Tl, the first widely available radiopharmaceutical for myocardial perfusion evaluation and the most commonly used in SPECT myocardial perfusion imaging. It has several advantages over the current technetium-99m myocardial perfusion agents, including a more physiological distribution because it is a potassium analog, a higher first-pass extraction, and the ability to keep up with blood flows at higher rates. Unlike 201Tl, technetium sestamibi and technetium-99m tetrofosmin have minimal redistribution. This redistribution property makes 201Tl superior to the technetium-99m myocardial perfusion agents for myocardial viability assessment.

The regression of thallium perfusion defects after DPM associated with the low frequency of stenosis in epicardial coronary arteries in asymptomatic patients (no chest pain, no angina pectoris) strongly supports the role of coronary microcirculation in these types of myocardial damage[7]. To our knowledge, until our study, myocardial impairment as a microcirculatory complication of TA had never been considered. Several microcirculatory complications in TA

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have been described in the literature, such as small cutaneous vessel necrotizing vasculitis[24,25], anterior ischemic optic neuropathy[26,27], small retinal vessel occlusions[28,29], and myocarditis[4,8,9]. Our results show that resting and DPM 201Tl myocardial scintigraphy could represent a useful noninvasive means for confirmation of cardiac involvement in TA. Its specificity is evidenced by a response to DPM different from that observed in CAD. The most likely explanation is the reversion of coronary microvascular vasoconstriction by DPM. Thus, this scintigraphic method could be relevant for assessment of coronary microvascular disease and quantification of myocardial perfusion in both large and small vessel vasculitis. Whereas cardiac involvement is a major prognostic factor in vasculitis, no cardiac imaging techniques have demonstrated to date a value to predict cardiac events. The current cardiac imaging technologies that are clinically available are unable to image vessels that are < 0.5 mm in diameter and thus the coronary microvasculature cannot be imaged *in vivo*. In the near future, we need to better identify pathophysiological mechanisms of cardiac involvement in vasculitis, to adequately examine cardiac functional abnormalities. In 8 patients with small vessel vasculitis [eosinophilic granulomatosis with polyangiitis (EGPA) or GPA] and 1 patient with vasculitis secondary to systemic lupus erythematosus, 2 studies described the usefulness of first-pass perfusion (FPP) MRI in the noninvasive assessment of the microvasculature in patients with acute cardiac involvement in primary and secondary vasculitis[30,31]. This MRI technique based on myocardial FPP imaging has not been tested in patients without cardiac symptoms.

Although the precise pathogenesis and significance of such myocardial ischemia is unclear, it appears to be more associated with specific features of TA, such as aortic regurgitation, renovascular hypertension, duration of disease, and male sex, than with traditional cardiovascular risk factors. Histological findings of the myocardial biopsy in patients with TA have demonstrated the presence of a lymphocytic infiltration. The natural killer cells and T lymphocyte–mediated autoimmunity may play major roles in vascular cell injury of TA by releasing perforin, a cytotoxic factor[32]. The inflammatory process in TA is predominantly found around the vasa vasorum and in the outer part of the media and the adventice, both nourished by the vasa vasorum. It has been reported that HLA expression is increased in the vasa vasorum of the aorta and in the walls of small myocardial vessels in patients with TA, and is also present on the ventricular myocytes[8,9,33]. The presence of HLA Bw52 antigen has been associated to a more severe left ventricle (LV) dysfunction in this disease[34]. Vasa vasorum, small cutaneous vessel, branched retinal arteries, and myocardial vessel have a similar diameter (< 150 μm), supporting the existence of microcirculatory lesions in myocarditis, as well as in cutaneous necrotizing vasculitis and retinal occlusion in TA. Myocardial perfusion defects in TA may be caused by specific inflammatory cardiac involvement of TA more than obstructive epicardial coronary arterial disease. The lack of cardiovascular risk factors, cardiac symptoms, significant Q waves, and segmental wall motion abnormalities in TA patients with myocardial perfusion defects supports our hypothesis.

Myocardial abnormalities have been frequently detected in several other autoimmune or inflammatory diseases. Eighty-two percent of myocardial ischemic disease have been found in SSc, 62% in Churg-Strauss syndrome, 44% in lupus, 29.6% in antiphospholipid syndrome, and 24% in sarcoidosis[35,36,37,38,39,40]. Interestingly, myocardial involvement in these diseases is often described as clinically silent and without coronary artery disease, suggesting the role of microcirculation impairment in myocardial dysfunction. Once cardiac involvement is clinically evident, it is recognized as a poor prognostic factor. Mortality is mainly the consequence of cardiac involvement[41,42,43]. Thus, it has become evident that early diagnosis and accurate staging of cardiac involvement are fundamental for appropriate management and therapeutic approaches for these diseases. Abnormalities in cardiac microcirculation have been investigated and established in patients with SSc and myocardial involvement, but with normal coronary angiography[44]. Studies using 201Tl scintigraphy have demonstrated that patients with SSc may benefit from the administration of the calcium channel blocker nifedipine, as well as intravenous DPM used as a pharmacodynamic test inducting maximal coronary artery vasodilation[17,18]. Indeed, the effects of such vasodilator agents improving myocardial perfusion further emphasize the key role of coronary microcirculation. However, the mechanisms of microvascular ischemia are probably different between SSc and TA. Further, not all abnormalities in myocardial perfusion in patients with TA may be reversible. The absence of regression of thallium perfusion defects after DPM may also be important to consider and to manage, to limit the progression of cardiac complications. The existence of myocardial scars induced by chronic vasoconstriction of coronary microcirculation could explain the absence of reversibility of thallium defects. We cannot exclude that some patients may have required a higher dosage of DPM to achieve full coronary vasodilation. Cardiac involvement due to associated coronary disease seems unlikely but cannot be totally disregarded in the absence of coronary arteriography in several of our patients (n = 14).

Our results demonstrate a high incidence of myocardial involvement in patients with TA mainly related to microcirculation impairment. This clearly demonstrates that this large vessel vasculitis also affects vessels of small size. Systematic cardiac evaluation including DPM 201Tl myocardial scintigraphy might be required to properly

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identify patients with TA who have asymptomatic myocardial involvement. Further studies are needed to determine whether myocardial findings using 201Tl myocardial scintigraphy and DPM as vasodilator have an effect on the prognosis and treatment strategy.

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