Rheumatol Int (2004) 24: 227–229
DOI 10.1007/s00296-003-0353-9

ORIGINAL ARTICLE

C. C. Lin · H. J. Ding · Y. W. Chen · J. J. Wang
S. T. Ho · A. Kao

High prevalence of asymptomatically poor muscle perfusion of lower extremities measured in systemic lupus erythematosus patients with abnormal myocardial perfusion

Received: 20 January 2003 / Accepted: 18 May 2003 / Published online: 15 July 2003

Abstract Patients with systemic lupus erythematosus (SLE) may develop premature atherosclerosis, notably peripheral vascular disease (PVD) presenting with intermittent claudication or gangrene. Therefore, it is important to investigate if high prevalence of poor muscle perfusion of lower extremities in SLE patients with abnormal myocardial perfusion is related to more cardiovascular risk factors. We used a well-established and noninvasive radionuclide method (xenon 133 muscle washout) to evaluate objectively the anterior tibial muscle perfusion of 34 SLE female patients without symptoms/signs of PVD in the lower extremities. The patients were separated into two groups according to myocardial perfusion imaging results. Meanwhile, 30 normal female controls with matched age distribution were also included for comparison. The muscle perfusion differed significantly ($P < 0.05$) between patients (1.90 ± 0.41 ml/100 g per min) and controls (2.91 ± 0.50 ml/100 g per min), as well as between 18 SLE patients with abnormal myocardial perfusion (1.33 ± 0.43 ml/100 g per min) and 16 with normal myocardial perfusion (2.26 ± 0.45 ml/100 g per min). Based on the xenon 133 muscle washout method, we conclude that muscle perfusion in the lower extremities of SLE patients without symptoms/signs of PVD is significantly decreased and related to abnormal myocardial perfusion.

Keywords Muscle perfusion · Myocardial perfusion · Systemic lupus erythematosus

C. C. Lin
Cardiovascular Division, Department of Internal Medicine,
Kaohsiung Medical University, Kaohsiung, Taiwan

H. J. Ding
Department of Medical Research,
School of Technology for Medical Sciences,
Kaohsiung Medical University, Kaohsiung, Taiwan

Y. W. Chen
Department of Nuclear Medicine,
Kaohsiung Medical University, Kaohsiung, Taiwan

J. J. Wang
Department of Medical Research,
Chi-Mei Medical Center, Tainan, Taiwan

S. T. Ho
Department of Anesthesiology,
Tri-Service General Hospital, Taipei, Taiwan

A. Kao (✉)
Department of Medical Research,
China Medical University Hospital,
No. 2 Yuh-Der Road, Taichung 404, Taiwan
E-mail: albertkaotw@yahoo.com.tw
Tel.: +886-4-22052121 ext 3475
Fax: +886-4-22023442

Introduction

Arterial vascular disease in systemic lupus erythematosus (SLE) has a number of pathogenic mechanisms including arteritis, intravascular coagulation frequently associated with a lupus anticoagulant [1] and, in chronic lupus, atherosclerosis [2]. The last mechanism is currently recognised as a major cause of death and morbidity in patients with SLE [3].

Arteriography is the gold but invasive standard for diagnosing occlusive arterial disease of the legs. It provides morphological data but no information about muscle perfusion, which depends on collateral circulation and the presence of small-vessel disease. When xenon (Xe)-133 (an inert gas can not react with tissues) diffuses from muscle of the lower extremities into the peripheral capillaries and reaches the lungs, it can be rapidly cleared without recirculation. Therefore, this clearance rate correlates with the blood perfusion that really reaches the muscle [4, 5]. In addition, poor muscle perfusion of lower extremities may result not only from macrovascular disease but also from microvascular disorders.

Therefore, in this study, we used an objective and noninvasive radionuclide method (Xe-133 muscle washout) to evaluate anterior tibial muscle perfusion of SLE patients without symptoms/signs of peripheral

vascular disease (PVD). In addition, we investigated whether there is a high prevalence of poor muscle perfusion of lower extremities in SLE patient subgroups with or without abnormal myocardial perfusion.

Patients and materials

Thirty-four female patients (age 45.0 ± 12.8 years) with SLE satisfying the American College of Rheumatology criteria [6] were included in this study. They were separated into subgroups according to myocardial perfusion imaging results: 18 with abnormal and 16 with normal myocardial perfusion. However, the two groups did not differ significantly in age, duration of SLE, partial thromboplastin time, antibodies to cardiolipin, lupus activity criteria count, mean steroid dose, mean duration of steroid use, or risk factors for developing PVD (such as smoking, hypertension, hyperlipidemia, and use of oral contraceptives) (Table 1). For comparison, 30 normal female controls (age 46.1 ± 12.1 years) with the same age distribution were also included. The inclusion criteria for all subjects were: absence of myocardial infarction and angina pectoris, normal results on 12-lead resting electrocardiography (ECG), and absence of PVD which was defined as one of intermittent claudication, absent peripheral pulses, gangrene, and angiographic or Doppler evidence of large vessel disease. None of the patients or controls had histories of stroke, congenital heart disease, cardiomyopathy, or vasculitis.

A one-day protocol of Tc-99m-sestamibi myocardial perfusion imaging during rest and stress after dipyridamole infusion (0.56 mg/kg over 4 min during ECG monitoring) was performed in all patients. Ten mCi and 25 mCi of Tc-99m-sestamibi were injected during rest and dipyridamole stress imaging, respectively. During the latter, Tc-99m-sestamibi was injected 2 min after the end of the infusion. All patients were instructed not to consume drugs or substances containing xanthine for 2 days before the study. Intravenous aminophylline was given 4 min after the Tc-99m-sestamibi, if patients had discomfort during dipyridamole infusion. Single photon emission computed tomography (SPECT) images were acquired 1 h after the Tc-99m-sestamibi injection using a large field of view, dual-headed, gamma camera equipped with a low-energy, all-purpose, parallel-hole collimator. Data were obtained from 64 projections of 25 s each in the 140 keV photopeak over a 180° arc in a 64×64 matrix. Short-axis, vertical long-axis, and horizontal long-axis images were reconstructed from the raw data by filtered back projection using a Butterworth filter with a cutoff frequency of 0.5 and order of 10 in the rest studies and cutoff frequency of 0.66 and order of 5 in the stress studies.

All images were interpreted blindly and separately by the agreement of at least two of three experienced nuclear medicine physicians. The imaging results were classified as normal or abnormal including persistent perfusion defect (present on both rest and dipyridamole stress images), reversible perfusion defect (present only on dipyridamole stress image), and reverse redistribution defect (demonstrated in the redistribution image and not in the stress image) [7, 8].

Each subject was allowed to rest for at least 30 min and acclimate to room temperature in the supine position under a digital gamma camera linked to a minicomputer. Approximately 0.1 ml (0.3–0.5 mCi) of Xe-133 dissolved in isotonic saline was slowly injected with a 27-gauge needle into the anterior tibial muscle (approximately 10 cm below the tibial tuberosity and 2 cm lateral to the tibia) of the right leg. The needle was held in place for at least 10 s to avoid Xe-133 leakage. The data were acquired simultaneously in a frame mode with 64×64 matrix at one frame/min for 20 min with a low-energy, parallel-hole collimator. A time-activity curve was generated from the region of interest at the site of injection. The power exponential fitting technique was used for curve fitting. The Xe-133 clearance half-time (T1/2) was measured from the power exponential fitted curve. Then the muscle perfusion was calculated ($Q = 0.7 \ln 2 \ 100 \text{ g muscle} \div T1/2$) [4, 5].

Statistical analyses were performed using SPSS software (SPSS, Chicago, Ill., USA). Anterior tibial muscle perfusion (ml/100 g per min) of the study groups and subgroups was expressed as mean ± standard deviation. Two-tailed independent Student's *t*-tests were used to evaluate the differences between study subgroups. *P* values of < 0.05 were considered significant.

Results

Based on the myocardial perfusion imaging results, the 34 female SLE patients were separated into (A) 18 patients with abnormal myocardial perfusion and (B) 16 with normal myocardial perfusion. The subgroup characteristics are listed in Table 1. Anterior tibial muscle perfusion in the normal female controls (2.91 ± 0.50 ml/100 g per min) was significantly higher than in the female SLE patients (1.90 ± 0.41 ml/100 g per min). Among the SLE patients, subgroup A patients with abnormal myocardial perfusion imaging results (1.33 ± 0.43 ml/100 g per min) had significantly poorer muscle perfusion than subgroup B patients with normal myocardial perfusion imaging results (2.26 ± 0.45 ml/100 g per min) (Table 2).

Discussion

As SLE patients survive longer, the morbidity patterns are changing [9]. Specifically, atherosclerotic complications involving coronary arteries have been reported. However, PVD due to atherosclerosis has only been

Table 1 Patient subgroup characteristics. *SLE* systemic lupus erythematosus, *PTT* partial thromboplastin time, *LACC* lupus activity criteria count

Parameters	Subgroup A	Subgroup B
N cases	18	16
Age (years)	45.6 ± 12.3	44.9 ± 11.7
Duration of SLE (years)	8.6 ± 1.3	9.0 ± 1.9
PTT (seconds)	31.5 ± 4.2	32.1 ± 5.6
LACC	0.74 ± 0.12	0.70 ± 0.11
Antibodies to cardiolipin	6 (33.3%)	5 (31.3%)
Mean steroid dose (mg prednisone/day)	13.5 ± 1.5	14.0 ± 1.2
Mean duration of steroid use (years)	8.3 ± 1.5	8.7 ± 1.6
Smoking	2/18 (11.1%)	2/16 (12.5%)
Hypertension	7/18 (38.9%)	6/16 (37.5%)
Hyperlipidemia	5/18 (27.8%)	5/16 (31.3%)
Use of oral contraceptives	6/18 (33.3%)	5/16 (31.3%)

Table 2 The anterior tibial muscle perfusion of the subgroup patients

Normal female controls	2.91 ± 0.50 ml/100 g per min
Female SLE patients	1.90 ± 0.41 ml/100 g per min)
Subgroup B SLE patients	1.33 ± 0.43 ml/100 g per min
Subgroup A SLE patients	2.26 ± 0.45 ml/100 g per min

rarely reported. After reviewing the literature, DePalma [10] described three patients with well-controlled SLE who developed symptomatic PVD of the feet. The patients had been treated with prednisone (5–12 mg daily) for 1–10 years. Other authors demonstrated that vasculitis of the foot usually was sudden, catastrophic, gangrenous, and accompanied by very active systemic disease [11, 12]. In addition, the general nature of atherosclerosis in SLE patients includes a combination of coronary artery disease and PVD [13]. Therefore, it could be expected that microvascular disease in SLE patients is likely to be systemic and associated with poor muscle perfusion of lower extremities and abnormal myocardial perfusion, as in our findings.

Histories of hypertension and smoking showed a trend towards increased frequency in those patients with PVD. Factors significantly related to the development of PVD included duration of SLE and corticosteroid use [13]. However, the two SLE subgroups in our study did not differ significantly in duration of SLE, classic therapy (mean steroid dose and duration of steroid use), or risk factors for developing PVD. Although at least six common indices (such as BILAG, ECLAM, LAI, SIS, SLAM, and SLEDAI) were routinely used to calculate the SLE activity, none of them focusses on cardiovascular involvement in SLE [14]. Thus, we did not calculate the SLE disease activity index to correlate the anterior tibial muscle perfusion by the Xe-133 washout technique in this study.

All of the 34 female SLE patients in our study had palpable pedal pulses, no resting pain, and intermittent claudication from large vessel occlusion in the lower extremities. Previously reported cases of atherosclerosis in SLE have described vasculitis, representing a vascular response to intimal proliferative lesions [13]. In addition, such lesions may be initiated by endothelial injury. However, subtle endothelial injury may be without morphological alteration. The Xe-133 washout technique can calculate individual muscle perfusion supplied by smaller vessels and differs from other modalities [4, 5] such as histological examinations, angiography, plethysmography, vital capillaroscopy, and Doppler echography, which can only detect either anatomic abnormalities of large vessels or the total blood flow in the capillary. Therefore, we can suppose that such small vessel disease might be involved in SLE patients with poor muscle perfusion of lower extremities as detected by Xe-133 washout but without significant PVD, demonstrated as a larger vessel disease detected by angiography or other modalities. In addition, we considered that the abnormal myocardial perfusion in SLE subgroup A was due to small vessel disease.

The objective and noninvasive Xe-133 washout technique may represent the actual muscle perfusion. It was proven to be useful for both early detection and research on the pathophysiology of microangiopathy in a subgroup of SLE patients with small vessel diseases. We conclude that muscle perfusion in the lower extremities of female SLE patients is lower, particularly in those with abnormal myocardial perfusion. However, in the present study, the Xe-133 injections were given in the right legs only. Therefore, we did not compare the difference in muscle perfusion between both legs of individual patients, and further investigation of this is necessary in a larger series.

References

1. Ansari A, Larson HP, Henry HD (1986) Vascular manifestations of systemic lupus erythematosus. Angiology 37:423–432
2. Tsakraklides MD, Blieden LC, Edwards JE (1974) Coronary atherosclerosis and myocardial infarction associated with systemic lupus erythematosus. Am Heart J 87:637–641
3. Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA (1976) The bimodal mortality pattern of systemic lupus erythematosus. Am J Med 60:221–225
4. Lin WY, Kao CH, Hsu CY, Liao SQ, Wang SJ, Yeh SH (1995) Evaluation of tissue perfusion by the Xe-133 washout method in lower limbs of patients with noninsulin-dependent diabetes mellitus. Clin Nucl Med 20:449–452
5. Tsou CT, Kao CH, Lin WY, Chen MD, Wang SJ, Lin WH, Ho LT (1993) The evaluation of blood perfusion of lower extremities in patients with NIDDM by 133Xe muscle clearance test: a preliminary report. Zhonghua Yi Xue Za Zhi 51:208–210
6. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277
7. Sun SS, Shiau YC, Tsai SC, Lin CC, Kao A, Lee CC (2001) The role of technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography (SPECT) in the detection of cardiovascular involvement in systemic lupus erythematosus patients with non-specific chest complaints. Rheumatology (Oxford) 40:1106–1111
8. Kao CH, Shen YY, Lee JK (1999) Effects of smoking on pulmonary uptake of technetium-99m methoxyisobutylisonitrile during myocardial perfusion imaging. J Nucl Cardiol 6:29–32
9. Gladman DD, Urowitz MB (1987) Morbidity in systemic lupus erythematosus. J Rheumatol 14:223–226
10. DePalma RG, Moskowitz RW, Holden WD (1972) Peripheral ischemia and collagen disease: clinical manifestations, diagnosis, and treatment. Arch Surg 105:313–318
11. Keat ECB, Shore JH (1958) Gangrene of the legs in disseminated lupus erythematosus. BMJ 1:25–27
12. Gladstein GS, Rynes RI, Parhami N, Bartholomew LE (1979) Gangrene of a foot secondary to systemic lupus erythematosus with large vessel vasculitis. J Rheumatol 6:549–553
13. McDonald J, Stewart J, Urowitz MB, Gladman DD (1992) Peripheral vascular disease in patients with systemic lupus erythematosus. Ann Rheum Dis 51:56–60
14. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P (1999) Outcome measures to be used in clinical trials in systemic lupus erythematosus. J Rheumatol 26:490–497