Baseline MRA predicts the treatment response to vasodilator udenafil in patients with secondary Raynaud's phenomenon

J.K. Park[1], E.-A. Park[2], W. Lee[2], Y.K. Kim[2], E.Y. Lee[1], Y.W. Song[1], E.B. Lee[1]

[1]*Department of Internal Medicine, and* [2]*Department of Radiology, Seoul National University College of Medicine, Seoul, Korea.*

Jin Kyun Park, MD
Eun-Ah Park, MD, PhD
Whal Lee, MD, PhD
Yeo Koon Kim, MD
Eun Young Lee, MD, PhD
Yeong Wook Song, MD, PhD
Eun Bong Lee, MD, PhD

Please address correspondence to:
Eun-Ah Park, MD, PhD,
Department of Radiology,
Seoul National University
College of Medicine,
101 Daehak-ro, Jongno-gu,
Seoul, 110-744, Korea.
E-mail: iameuna1@gmail.com

Received on March 27, 2014; accepted in revised form on May 26, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 86): S167-S170.

Key words: Raynaud's phenomenon, vasodilator, MRA, Doppler ultrasound, treatment response

Funding: this investigator-initiated study was supported by Dong-A Pharmaceutics. However, the sponsor was not involved in the design, conduction, or interpretation of the study. None of the authors have any commercial benefits or financial interests in the work reported.

Competing interests: none declared.

ABSTRACT

Objective. *High-resolution MR angiography (HR-MRA) demonstrates blood flow in the digital arteries, which correlates with the severity of Raynaud's phenomenon (RP). This study investigates whether baseline HR-MRA of the hand can predict the treatment response to udenafil, a new PDE5-inhibitor, in patients with secondary RP.*

Methods. *Baseline MRA and Doppler ultrasound were obtained in 12 patients with secondary RP. The patients were treated with udenafil 100 mg/day for 4 weeks and changes in blood flow were measured. Blood flow on MRA was scored on a 4-point scale: 0, no visible flow; 1, visible flow to the proximal phalanx; 2, to the middle phalanx; and 3, to the distal phalanx. Peak systolic velocity (PSV) was measured to determine blood flow. Paired t-test and ANOVA were used to determine the treatment response of the different MRA scores.*

Results. *On baseline MRA, 53.3% of digital arteries had an MRA score of 0, 25.8% MRA score of 1, 9.2% MRA score of 2, and 11.6% MRA score of 3. Overall, 4-week udenafil treatment improved digital flow ($p<0.05$) in all MRA scores. Digital arteries with MRA score 2 showed the best response with improvement in PSV by 14.5 mm/sec ($p<0.01$), whereas improvement in arteries of MRA scores 1 and 3 were not better than an MRA score of 0 (all, $p>0.05$).*

Conclusion. *Digital arteries with moderate blood flow observed on MRA respond best to treatment with udenalfil. Therefore, baseline MRA may help predict treatment response in patients with secondary RP.*

Introduction

Primary Raynaud's phenomenon (RP), a reversible vasospasm, is commonly observed in the general population without much clinical significance. To the contrary, secondary RP associated with underlying rheumatic diseases can lead to severe tissue ischaemia with tissue necrosis and debilitating morbidity (1, 2). Extensive injuries of yet-to-define mechanisms to the vascular wall with subsequent functional and structural changes of digital arteries are thought to contribute to secondary RP (3-5). While keeping one's hands warm and avoidance of cold exposure are often enough to abrogate RP attacks in primary RP patients, vasospastic attacks in patients with secondary RP can last long with substantial morbidity, often requiring treatment with vasodilators. Among vasodilators, the phosphodiesterase type 5 (PGE5) inhibitor, which increased the level of cGMP in vascular smooth muscle cells, showed good efficacy in improving blood flow and accelerating the healing process of digital ulcers in secondary RP patients (6-8). Since udenafil as a new reversible selective PGE5 inhibitor has rapid onset and relatively long duration of action with T1/2 of 7.3–12.1 hours, it is an attractive candidate for the treatment of RP (8).

High resolution three-dimensional MR angiography (HR-3D-MRA) is now capable of accurately demonstrating blood flow in the digital arteries, which correlates with the duration and severity of RP (9, 10). As vasodilation or reversion of vasospasms is an active process requiring the function of all vascular wall layers, it is conceivable that structural damages to the vascular wall in secondary RP may limit the vascular response to vasodilators. Thus, arteries with severe structural changes and fixed lesions would respond less to vasodilators, whereas vessels with non-fixed, moderate vasoconstriction may respond better to treatment and intact arteries with no vasoconstriction would respond only modestly.

Therefore, in our study, we hypothesised that baseline structural changes of the digital arteries seen on MRA would be able to predict their response to vasodilator udenafil, a new PDE5-inhibitor.

Methods

This study was designed as a sub-study of the previously published double-blinded cross over study comparing the efficacy of udenafil and amlodipine (8). The present study was specifically designed to investigate the value of baseline MRA in predicting the response to the vasodilator udenafil or amlodipine in patients with secondary RP. As amlodipine did not show any efficacy in improving digital flow, only data from the udenafil group were analysed (8). This study was registered at Clinicaltrials.gov under the protocol number NCT01280266. The study protocol was approved by Institutional Review Board and informed consents were obtained from all patients.

Study participants

RP patients associated with connective tissue disease who were 18 or older and had moderate to severe RP were included. The presence of concurrent infections of digits, an allergic reaction to a PDE5 inhibitor, a history of coronary artery disease or cerebrovascular disease, BP <90/50 mm Hg, or >170/100 mm Hg were excluded.

Study protocol

At baseline, MRA of the more severely affected hand was obtained at a 3-T imager (TIM Trio; Siemens, Erlangen, Germany) with a flexible surface coil. Gadolinium-enhanced imaging (0.1 mmol/kg, gadopentetate dimeglumine, Magnevist; Schering, Berlin, Germany) was performed using a 3D gradient echo sequence with images acquired in the hand's coronal plane (TE 5.0 msec/TR 1.7 msec; flip angle; 0.5x0.5 mm^2 in-plane resolution, 0.7 mm slice thickness). Acquisition time for the whole 3D volume was 20 sec. Blood flow in all 10 proper palmar digital arteries (PPDAs) arising from the common palmar digital arteries in each hand was scored based on the presence of visible flow using a 4-point scale: 0, no visible flow; 1, visible flow to the level of the proximal phalanx; 2, visible flow to the middle phalanx; and 3, visible flow to the distal phalanx (Fig. 1).

Using Doppler ultrasound (Accuvix XG; Samsung Medison, Seoul, Korea), peak systolic velocity (PSV, cm/sec) of blood flow in the digital arteries was measured in each of the 10 PPDAs of the same hand before and after administration of udenafil 100 mg/day for 4 weeks. None of the patients experienced an RP attack during the MRA or Doppler ultrasound examinations.

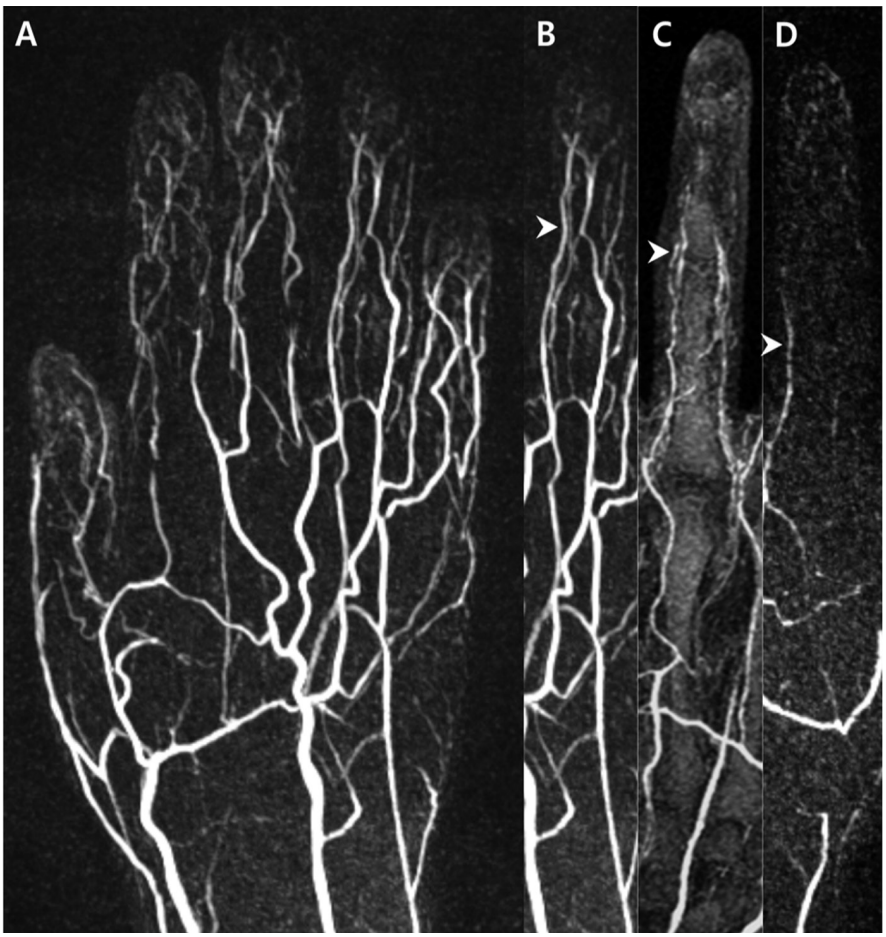

Fig. 1. Scoring of blood flow of the proper palmar digital artery on MR angiography (MRA). 3T arterial maximum intensity projection image shows multi-segmental, high-grade stenosis of the proper palmar digital arteries (**A**). MRA scores 3, 2, and 1 were defined by the presence of visible flow at the level of the distal (**B**: arrowhead), middle (**C**: arrowhead) or proximal phalanx (D: arrowhead), respectively. Non-visible flow indicates score 0 (**D**, the radial side of the proper palmar digital artery).

Statistical analysis

The paired *t*-test was used to compare blood flow before and 4 weeks after administration of udenafil. Improvements in PSV among all four MRA groups were compared using one-way analysis of variance (ANOVA) and Bonferroni-Dunn posthoc tests for multiple comparisions. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using a software package (SPSS 16.0; SPSS, Chicago, Ill).

Results

Patient demographics

A total of 12 patients were analysed in this study (Table I). Their mean age was 52.3±10.3 years with a female dominance of 91.7% (11/12). The mean duration of RP was 5.6±2.3 years.

Baseline MRA

Blood flow was not visualised in 64 (53.3%) of 120 PPDAs. In 31 (25.8%) PPDAs the flow was visible at the level of the proximal phalanx. The flow was visualised at the level of the middle and distal phalanx were only in 11 (9.2%) and 14 (11.6%) in PPDAs, respectively, reflecting that our enrolled patients had moderate to severe luminal changes.

Improvement in digital flow according to MRA score

The primary end-point of our study

Table I. Study population.

	n=12
Age, mean ± SD (yrs)	52.3 ± 10.3
Female sex, n (%)	11 (91.7)
CTD subtype, n (%)	
LcSSc	2 (16.7)
DcSS	7 (58.3)
MCTD	2 (16.7)
Sjögren's disease	1 (8.3)
CTD duration, mean ± SD (yrs)	5.1 ± 5.3
RP duration, mean ± SD (yrs)	5.6 ± 2.3
Smoker, n (%)	0 (0)
Prior use of vasodilators*, n (%)	
CCB	4 (33.3)
Pentoxifylline	1 (8.3)

*All patients stopped vasodilators on average 2 weeks prior to the study begin. CTD: connective tissue disease; RP: Raynaud's phenomenon; Yrs: years; LcSSc: localised systemic sclerosis; DcSS: diffuse cutaneous systemic sclerosis; MCTD: mixed connective tissue disease; SD: standard deviation.

Table II. Improvements in blood flow in the digital arteries according to MRA score. Peak systolic velocities (PSVs) were measured before and after udenafil administration for 4 weeks in each of the10 proper palmar digital arteries of the 12 patients.

MRA score	n. (%) n=120	PSV before (mm/sec)	PSV after (mm/sec)	Mean difference (mm/sec)	*p*-value
0	64 (53.3)	26.1 ± 12.3	29.6 ± 12.7	3.5 ± 1.5	**0.024**
1	31 (25.8)	26.6 ± 10.6	33.1 ± 12.0	6.4 ± 9.7	**0.001**
2	11 (9.2)	25.7 ± 15.7	40.3 ± 17.7	14.5 ± 14.0	**0.006**
3	14 (11.6)	20.8 ± 14.0	29.1 ± 20.7	8.2 ± 10.9	**0.014**

Numbers represent mean ± standard deviation.

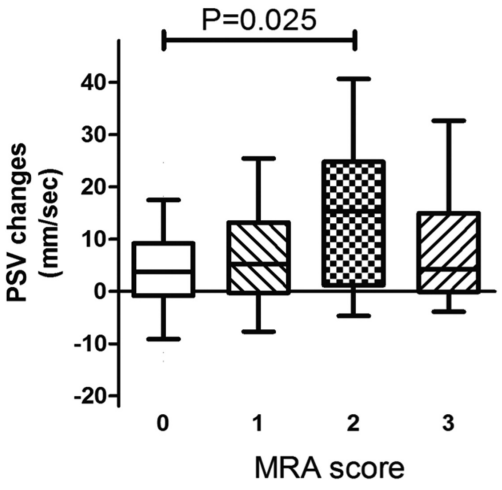

Fig. 2. Improvements in digital flow according to different baseline MRA scores. The group with moderate structural changes (*i.e.* group with an MRA score of 2) showed the best response to the vasodilator shown as changes in peak systolic velocity (PSV) from baseline. Whiskers represent 5 and 95 percentiles.

was improvement in the blood flow of each digital artery to the level of the proximal digital arteries after treatment with udenafil. Indeed, the digital flow of all MRA subgroups improved significantly after udenafil treatment for 4 weeks (Table II).

Best response in arteries with moderate structural changes on baseline MRA

PPDAs of the different MRA scores responded differently to the vasodilator (p=0.027, ANOVA); the RP group with an MRA score of 2 showed the best response compared to the groups of other MRA scores (p=0.025). There was no statistical difference between any other groups (Fig. 2).

Discussion

Our findings demonstrate that baseline luminal changes on MRA are associated with the improvement in digital blood flow in response to the vasodilator udenafil, with the best response observed in arteries of moderate luminal changes.

In patients with secondary RP associated with rheumatic diseases, the severity of RP might reflect the extent of vasculopathy-associated structural changes of vessel walls and abnormal vasoconstrictory response. Indeed, endothelial cell dysfunction in systemic lupus erythematosus, systemic sclerosis, and atherosclerosis leads to impaired relaxation of smooth muscle cells in response to nitric oxide (11-14). It should be emphasised that blood flow in the digital arteries seen on MRA may only reflect the changes in luminal diameter as a product of both reversible vasoconstriction and irreversible, fixed structural changes including intimal hyperplasia as a result of vascular remodelling (15). Although histologic correlation is yet to be established, it is tempting to speculate that the MRA score 0 group might have advanced structural changes with more fixed lesions, whereas the MRA score 2 group might have more reversible components contributing to decreased luminal diameters. Indeed, the best response was observed in those with moderate MRA scores. Arteries with an MRA score of 3 with good visible perfusion in the distal finger showed only modest response to the vasodilator as those vessels may have only trivial reversible vasoconstrictions at baseline. Moreover, as MRA and Doppler-sonography were obtained at a time when patients were not experiencing any acute RP attacks, the decreased luminal caliber and blood flow observed in our study may reflect the chronic state of vasculopathy as a combination of vascular remodelling and/or persistent vasoconstriction due to chronic vascular dysfunction in secondary RP.

This study has several limitations. First, repeat MRAs were not obtained after 4 week treatment with the vasodilator. Thus, it remains to be established whether improvement in the digital flow on Doppler sonograms can be translated into findings on MRA since fixed structural lesions may persist. Second, it remains to be defined whether arterial blood flow measured as PSV truly correlates with arterial lumen size on MRA since blood flow is the result of a complex interplay of numerous factors including capillary and venous resistance in addition to luminal diameters and arterial blood pressure. Last but not least, our study included a relatively small sample size and therefore further studies with a larger cohort are warranted.

Conclusions

Digital arteries with moderate luminal changes observed on MRA respond best to treatment with udenalfil. Therefore, baseline MRA may help predict treatment response in patients with secondary RP.

References

1. WIGLEY FM: Clinical practice. Raynaud's phenomenon. *N Engl J Med* 2002; 347: 1001-8.
2. BOIN F, WIGLEY FM: Understanding, assessing and treating Raynaud's phenomenon. *Curr Opin Rheumatol* 2005; 17: 752-60.
3. FREEMONT AJ, HOYLAND J, FIELDING P, HODSON N, JAYSON MI: Studies of the microvascular endothelium in uninvolved skin of patients with systemic sclerosis: direct evidence for a generalized microangiopathy. *Br J Dermatol* 1992; 126: 561-8.
4. BLANN AD, ILLINGWORTH K, JAYSON MI: Mechanisms of endothelial cell damage in systemic sclerosis and Raynaud's phenomenon. *J Rheumatol* 1993; 20: 1325-30.
5. PRESCOTT RJ, FREEMONT AJ, JONES CJ, HOYLAND J, FIELDING P: Sequential dermal microvascular and perivascular changes in the development of scleroderma. *J Pathol* 1992; 166: 255-63.
6. FRIES R, SHARIAT K, VON WILMOWSKY H, BOHM M: Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; 112: 2980-5.
7. DE LAVEGA AJ, DERK CT: Phosphodiesterase-5 inhibitors for the treatment of Raynaud's: a novel indication. *Expert Opin Investig Drugs* 2009; 18: 23-9.
8. LEE EY, PARK JK, LEE W *et al*.: Head-to-head comparison of udenafil vs amlodipine in the treatment of secondary Raynaud's phenomenon: a double-blind, randomized, cross-over study. *Rheumatology* (Oxford) 2014; 53: 658-64.
9. ZHANG W, XU JR, LU Q, YE S, LIU XS: High-resolution magnetic resonance angiography of digital arteries in SSc patients on 3 Tesla: preliminary study. *Rheumatology* (Oxford) 2011; 50: 1712-9.
10. WALCHER J, STRECKER R, GOLDACKER S, WINTERER J, LANGER M, BLEY TA: High resolution 3 Tesla contrast-enhanced MR angiography of the hands in Raynaud's disease. *Clin Rheumatol* 2007; 26: 587-9.
11. ANDERSON TJ, GERHARD MD, MEREDITH IT *et al*.: Systemic nature of endothelial dysfunction in atherosclerosis. *Am J Cardiol* 1995; 75: 71B-74B.
12. THACKER SG, ZHAO W, SMITH CK *et al*.: Type I interferons modulate vascular function, repair, thrombosis, and plaque progression in murine models of lupus and atherosclerosis. *Arthritis Rheum* 2012; 64: 2975-85.
13. MANETTI M, GUIDUCCI S, ROMANO E *et al*.: Overexpression of VEGF165b, an inhibitory splice variant of vascular endothelial growth factor, leads to insufficient angiogenesis in patients with systemic sclerosis. *Circulation Res* 2011; 109: e14-26.
14. DISTLER JH, GAY S, DISTLER O: Angiogenesis and vasculogenesis in systemic sclerosis. *Rheumatology* (Oxford) 2006; 45 (Suppl. 3): iii26-27.
15. KAHALEH MB: Endothelin, an endothelial-dependent vasoconstrictor in scleroderma. Enhanced production and profibrotic action. *Arthritis Rheum* 1991; 34: 978-83.