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CASE REPORT
Other

Finger blood flow after the cold challenge with primary Raynaud's syndrome: a case report

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Background Raynaud's syndrome is a commonly encountered disorder. The relationship between the grade of Raynaud's phenomenon and severity of vasoconstriction is unclear. Recently, various methods including colour Doppler ultrasonography have been used for assessment of vascularity of the extremities including fingers.

Case summary A 53-year-old man had a 6-year history of Raynaud's phenomenon with typical tri-coloured changes proceeding from white, blue to red and slight pain and slight paresthaesia in the fingers of both hands when his fingers were exposed to cold. He was diagnosed with primary Raynaud's syndrome. After treatment with the calcium channel blocker amlodipine (5 mg once daily), a cold challenge did not induce Raynaud's phenomenon on the fingers in the present patient. After the cold challenge, colour Doppler ultrasonography showed that vascularity was markedly decreased or was absent, whereas there was little difference in skin colour of the fingers.

Discussion In Raynaud's phenomenon, vasospasm may occur even if the symptoms are well-controlled with a calcium channel blocker. It is unlikely that clinical symptoms in patients with Raynaud's syndrome always reflect the severity of vasoconstriction in their fingers.

Keywords Raynaud's syndrome • Cold challenge • Finger blood flow • Colour Doppler ultrasonography • Calcium channel blocker • Case report

Learning points

- In Raynaud's phenomenon, vasospasm may occur even if the symptoms are controlled well with a calcium channel blocker.
- Non-invasive colour Doppler ultrasonography examination is useful for evaluation of the condition of vascularity in a finger.
- It is unlikely that clinical symptoms in the fingers of patients with Raynaud's syndrome always reflect the severity of vasoconstriction in their fingers.

Introduction

Raynaud's syndrome is a commonly encountered disorder. Typical episodes of Raynaud's phenomenon are skin colour changes in pallor and cyanosis in the extremities following cold exposure or emotional stress.[1,2] It is thought that the mechanisms of Raynaud's phenomenon are due to acute onsets of vasospasm-induced ischaemia and sympathetic nervous system activation-induced vasoconstriction in small finger arteries.[3] However, the precise mechanisms by which cold exposure and emotional stress induce Raynaud's phenomenon remain

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unknown. In addition, the relationship between the grade of Raynaud's phenomenon and severity of vasoconstriction is unclear. Recently, various methods including colour Doppler ultrasonography have been used for assessment of vascularity of the extremities including fingers.[4–6]

We present that a case of cold exposure inducing vasoconstriction without clinical symptoms in a patient with primary Raynaud's syndrome who was receiving a calcium channel blocker.

Timeline

Time	Events
6 years ago	The patient was diagnosed with primary Raynaud's syndrome during his routine medical check-up, and treatment with amlodipine was started at a dose of 5 mg per day
Follow-up (5 years)	Although the patient had no typical Raynaud's phenomenon, the patient sometimes had slight paresthaesia when exposed to cold, especially in winter

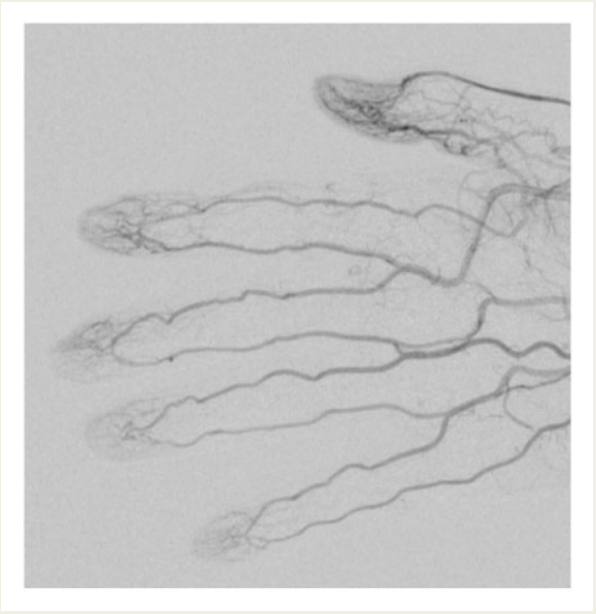

Figure 1 Digital subtraction angiography in the fingers of the right hand. Digital subtraction angiography showed no stenosis or obstructive lesions in the fingers of the right hand.

Case presentation

A 53-year-old man had a 6-year history of Raynaud's phenomenon with typical tri-coloured changes proceeding from white, blue to red and slight pain and slight paresthaesia in the fingers of both hands when his fingers were exposed to cold and he had no history of digital pitting, ulcers, or gangrene.

The patient did not have hypertension, dyslipidaemia, diabetes mellitus, a history of cardiovascular disease, or a smoking habit. His past medical history was clear. On admission, all of the laboratory findings were within normal ranges. Results of rheumatoid factor, lupus anticoagulants, and serologic investigations were also within normal ranges. He had no abnormal results of cardiovascular examinations including chest X-ray, electrocardiography and echocardiography, or abnormal physical findings. Digital subtraction angiography showed no stenosis or obstructive lesions in any of the fingers of either hand. *Figure 1* shows angiography in the right hand. His ankle brachial blood pressure indices were 1.10 on the right side and 1.09 on the left side. He was diagnosed with primary Raynaud's syndrome.

After treatment with the calcium channel blocker amlodipine (5 mg once daily), he had no typical Raynaud's phenomenon. However, he sometimes had slight paresthaesia when exposed to cold, especially in winter. Thus, we performed a cold challenge (by having the patient place his right hand in water with a temperature of 10°C for 5 min). Although the cold challenge did not induce Raynaud's phenomenon, he had slight paresthaesia and slight pain in all five fingers during and for ~15 min after the cold challenge. Before the cold challenge, normal vascularity in the right hand was visualized by a transverse scan of the fingertips (*Figure 2A* and Supplementary material online, *Videos S1–S3*, asterisks) using colour Doppler ultrasonography [Aloka prosound α7 (Hitachi Healthcare, Tokyo, Japan); probe type, linear transducer (13.3–3.61 MHz); imaging frequency, 5 MHz]. After 3 min of the cold challenge, vascularity was markedly decreased or was absent in all five fingertips (*Figure 2B* and Supplementary material online, *Videos S4–S6*, asterisks), whereas there was little difference in skin colour of his hands and fingers before and after the cold challenge (*Figure 2A and B*). The therapy using the calcium channel blocker amlodipine did not differ since the symptoms disappeared after taking care the exposure to cold within a 6-year follow-up period.

Discussion

Management of and therapy for Raynaud's phenomenon in patients with primary Raynaud's syndrome have not been established. Calcium channel blockers are commonly used for prevention of vasospasm in these patients.[7] In the present patient also, treatment with the calcium channel blocker amlodipine improved clinical symptoms of Raynaud's phenomenon. Even after a cold challenge under the condition of treatment with amlodipine, he had no typical Raynaud's phenomenon. However, colour Doppler ultrasonography revealed cold exposure-induced reduction in finger blood flow, suggesting that vasospasm exists under the condition of well-controlled Raynaud's phenomenon by treatment with amlodipine. In patients unresponsive to first-line therapy with a calcium channel blocker, the use of phosphodiesterase type 5 inhibitors, prostanoids, and endothelin inhibitors should be considered as second-line therapy. If clinical symptoms get worse in patients unresponsive to conventional therapy, digital sympathectomy should finally be considered for such

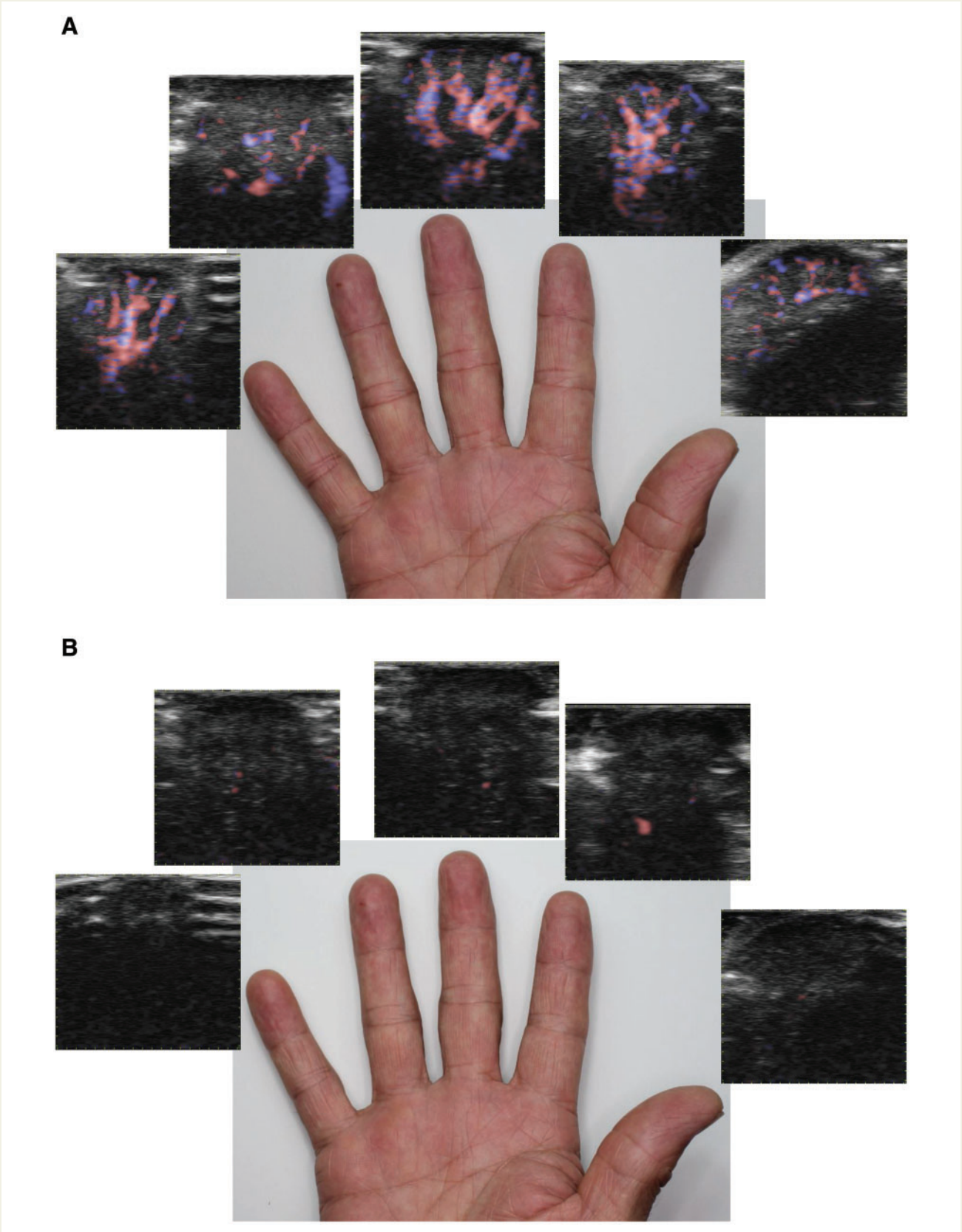

Figure 2 Blood flow in the fingers of the right hand before and after a cold challenge. Before a cold challenge, normal vascularity in the right hand was visualized by a transverse scan of the fingertips (*A*, see Supplementary material online, *Videos S1–S3*, asterisks) using colour Doppler ultrasound. After the cold challenge, vascularity was extremely decreased or was absent (*B*, see Supplementary material online, *Videos S4–S6*, asterisks), whereas there was little difference in skin colour of the hands and fingers before and after the cold challenge (*A* and *B*).

patients. However, the efficacy of sympathectomy is generally limited and often does not last long, only a few years.

Although the reason for no typical Raynaud's phenomenon despite the existence of severe vasospasm remains unclear, we should pay attention to the possibility of a discrepancy in clinical symptoms and findings of vascular structure and function in patients with Raynaud's syndrome. It is well known that the network in the skin is constructed by two horizontal superficial arteriovenous plexuses, the subcutaneous plexus and papillary plexus, a capillary loop located in the papillary layer as a terminal artery, and arteriovenous anastomoses. These vessels exist 1.0–1.5 mm below the skin surface and modulate skin temperature by regulation of blood flow.[8] Interestingly, cold-induced vasodilation is induced by an increase in blood flow at the sites of arteriovenous anastomoses in the skin.[9] There is a possibility that blood supply to the skin in the present patient was maintained through bypass vessels in the microcirculation network under the condition of cold exposure. As shown in *Figure 2* and Supplementary material online, *Figures S1–S6*, we can see the small arteries in the finger using colour Doppler ultrasonography. However, it is difficult to accurately assess the blood flow in the arteriole after the small artery. Measurement of blood flow in the subcutaneous plexus, papillary plexus, and capillary loop during a cold challenge test would enable more specific conclusions concerning the relationships between bold flow in the arteriole and clinical symptoms to be drawn. As has been shown in a number of studies including our study,[4–6]non-invasive colour Doppler ultrasonography examination is useful for evaluation of the condition of vascularity in a finger.

Some possibilities for the pathophysiology of Raynaud's phenomenon are postulated. Vasoconstriction induced by vasospasm or abnormality of the sympathetic nervous system should be a key regulator of Raynaud's phenomenon.[3] In addition, it is thought that endothelial dysfunction might contribute to Raynaud's phenomenon through inactivation of the nitric oxide/endothelial nitric oxide synthase pathway. However, the present patient had normal endothelial function as assessed by a flow-mediated vasodilation value of 7.4%. Recently, we have proposed that the cut-off value for normal endothelial function assessed by flow-mediated vasodilation of the brachial artery is 7.1% in Japanese.[10]

We should know three types of vascular conditions in a finger under the condition of treatment with a calcium channel blocker after cold exposure in patients with Raynaud's syndrome: (i) lack of symptoms without vasoconstriction in all of the digital arteries, (ii) lack of symptoms with vasoconstriction in digital small arteries but not in microcirculation, and (iii) symptoms with vasoconstriction. Although there is no evidence indicating how a patient with a significant decrease in finger blood flow after a cold exposure test despite lack of symptoms should be treated, additional treatment should be considered to prevent future complications such as gangrene and ulcers on the fingertips.

We simply performed lower extremity angiography and coronary angiography as well as upper extremity angiography and confirmed no structural stenosis in his peripheral arteries and coronary arteries. We did not perform any clinical assessment regarding the possible occurrence of spasms, including provocative testing for coronary reactivity and spasm, in the coronary artery and lower extremity artery since there were no episodes of spasms of the peripheral artery and coronary artery other than the hands.

Conclusions

Treatment with the calcium channel blocker amlodipine improved Raynaud's phenomenon in the fingers of a patient with primary Raynaud's syndrome. Cold exposure induced vasoconstriction without clinical symptoms under the condition of well-controlled Raynaud's phenomenon by treatment with the calcium channel blocker. It is unlikely that clinical symptoms in patients with Raynaud's syndrome always reflect the severity of vasoconstriction in their fingers.

Lead author biography

Yukihito Higashi, MD, PhD, FAHA, is an expert in the diagnosis and treatment of cardiovascular diseases, including hypertension, dyslipidaemia, atherosclerosis, peripheral arterial disease, and coronary artery disease. He specializes in non-invasive cardiology using advanced techniques and novel clinical markers to assess vascular function, particularly endothelial function. He also tries to angiogenesis in patients with critical limb ischaemia. He is currently the Professor and Chair in the Department of Cardiovascular Regeneration and Medicine in Research Institute for Radiation Biology and Medicine at the Hiroshima University, Hiroshima, Japan.

Supplemental material

Supplemental material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References

1. Raynaud M. *On Local Asphyxia and Symmetrical Gangrene of Extremities*. T Barlow, trans. London: The Sydenham Society; 1888.
2. Wigley FM, Flavahan NA. Raynaud's Phenomenon. *N Engl J Med* 2016;**375**: 556–565.

3. Herrick AL. Pathogenesis of Raynaud's phenomenon. *Rheumatology (Oxford)* 2005;**44**:587–596.
4. Herrick AL, Clark S. Quantifying digital vascular disease in patients with primary Raynaud's phenomenon and systemic sclerosis. *Ann Rheum Dis* 1998;**57**:70–78.
5. Keberle M, Tony HP, Jahns R, Hau M, Haerten R, Jenett M. Assessment of microvascular changes in Raynaud's phenomenon and connective tissue disease using colour Doppler ultrasound. *Rheumatology (Oxford)* 2000;**39**: 1206–1213.
6. Fujii Y, Soga J, Hidaka T, Hata T, Idei N, Fujimura N et al. Color Doppler flows of corkscrew collaterals in thromboangiitis obliterans (Buerger disease) using color duplex ultrasonography. *J Am Coll Cardiol* 2011;**57**:2539.
7. Ennis H, Hughes M, Anderson ME, Wilkinson J, Herrick AL. Calcium channel blockers for primary Raynaud's phenomenon. *Cochrane Database Syst Rev* 2016;**2**: CD002069.
8. Braverman IM. The cutaneous microcirculation: ultrastructure and microanatomical organization. *Microcirculation* 1997;**4**:329–340.
9. Fox RH, Wyatt HT. Cold-induced vasodilatation in various areas of the body surface of man. *J Physiol* 1962;**162**:289–297.
10. Maruhashi T, Kajikawa M, Kishimoto S, Hashimoto H, Takaeko Y, Yamaji T et al. Diagnostic criteria of flow-mediated vasodilation for normal endothelial function and nitroglycerine-induced vasodilation for normal vascular smooth muscle function of the brachial artery. *J Am Heart Assoc* 2020;**9**:e013915.