The use of hand perfusion scintigraphy to assess Raynaud's phenomenon associated with hand-arm vibration syndrome

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Received on February 22, 2017; accepted in revised form on June 19, 2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 106): S138-S143.

Key words: Raynaud's phenomenon, hand perfusion scintigraphy, hand-arm vibration syndrome, systemic sclerosis

Competing interests: none declared.

ABSTRACT

Objective. *This study aimed to evaluate the hand perfusion scintigraphic features of hand-arm vibration syndrome (HAVS) and to compare these with the features of primary and secondary Raynaud's phenomenon (RP) associated with systemic sclerosis (SSc).*

Methods. *Hand perfusion scintigraphy was performed in 57 patients with primary RP, 71 patients with HAVS-related RP, and 15 patients with SSc-related RP. We calculated 6 ratios: chilled to ambient hand and wrist ratios of the first peak height, initial slope, and blood pool uptake. We analysed 3 morphologic characteristics: slow progress pattern, paradoxically increased uptake pattern, and inhomogeneous radioactivity uptake.*

Results. *All of the 71 patients with HAVS-related RP were mine workers. The chilled to ambient hand ratios of the first peak height, the initial slope, and the blood pool uptake were significantly lower in patients with HAVS-related occupational RP than in patients with primary RP. The presence of a paradoxically increased uptake pattern was significantly lower in HAVS than in primary RP.*

Conclusion. *There were significant differences in hand perfusion scintigraphic features between primary RP and HAVS. These results suggest that the underlying pathophysiology of the two diseases differs.*

Introduction

Hand-arm vibration syndrome (HAVS) is a complex and potentially disabling chronic disorder of the upper extremities, which occurs following prolonged exposure to hand-transmitted vibrations. HAVS affects patients' quality of life, their ability to work, and their general health (1-3). Therefore, there has been renewed interest in the early recognition, accurate diagnosis, and proper management of HAVS. HAVS is divided into vascular, sensorineural, and muscular components. Raynaud's phenomenon (RP) is the most common manifestation of HAVS (4).

Raynaud's phenomenon is characterised by reversible and episodic vasospasm of the extremities in response to stress or exposure to cold. RP is classified as primary when it occurs without evidence of underlying diseases, or as secondary when it is associated with other diseases. The majority of these tend to be connective tissue diseases (CTD), but RP is also associated with veno-occlusive diseases, malignancies, endocrine diseases, certain drugs, as well as with many occupational and environmental factors (5-7, 9).

A subjective description of the clinical manifestations of RP provided by workers may not always be accurate and reliable enough to diagnose this condition, especially when medico-legal and economic issues are involved. Therefore, many objective tests have been developed in order to aid clinicians to formulate an accurate and reliable diagnosis of RP, including finger systolic blood pressure measurement after cold water provocation, arteriography, thermography, Doppler ultrasound, and hand perfusion scintigraphy (5, 8-11). Hand perfusion scintigraphy is a non-invasive and quantitative method to evaluate RP. The sensitivity and specificity of digital blood flow scintigraphy for RP are 81-91.2%, and 88-94%, respectively (10, 12). For these reasons, hand perfusion scintigraphy is commonly used as a diagnostic tool for RP.

Previous studies have evaluated the diagnostic validity and characteristics of hand perfusion scintigraphy. However, no study to date has classified or differentiated the findings of this technique based on the aetiology of RP. This

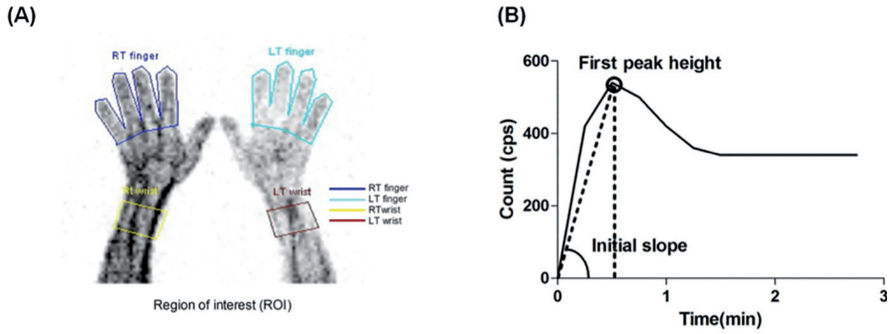

Fig. 1. Hand perfusion scintigraphy with one hand chilling in a patient with Raynaud's phenomenon. (**a**) Regions of interest for the fingers (excluding the thumb) and the wrist of both hands on the blood pool image are demonstrated. (**b**) The first peak height and initial slope were measured from the time–activity curve of the blood flow images. The initial slope was assessed from the angle made by the x-axis and the line from the initial peak.

study aimed to compare the hand perfusion scintigraphic features of HAVS-related RP, primary RP, and systemic sclerosis (SSc)-related RP.

Methods

Study design and study population

We performed a retrospective review of medical records to identify patients with a diagnosis of RP who underwent hand perfusion scintigraphy at Konkuk Medical Centre between March 2005 and February 2016. All patients with RP had a clinical history of cold-induced pallor of the hands, followed by cyanosis or erythema on rewarming, which had been confirmed with photographs or by a physician. Patients with primary Raynaud's disease fulfilled 2014 international consensus criteria for the diagnosis of primary RP (13). The HAVS group had a history of extensive occupational vibration exposure and developed HAVS symptoms including RP, in the absence of other potential underlying causes of RP. The diagnosis of SSc was made in accordance with the American College of Rheumatoid Arthritis/European League Against Rheumatism (ACR/EULAR) criteria (14).

We performed laboratory tests for blood biochemical profiling including thyroid function tests, as well as quantification of anti-nuclear antibody, rheumatoid factor, anti-centromere antibody, and anti-scl70 antibody levels. In cases of suspected underlying CTD, additional autoantibody tests were performed in order to help us distinguish primary from secondary RP. Patients were excluded if they had an overlapping diagnosis of occupational or CTD-related RP, were taking vasoactive drugs, or if data about the onset of RP and duration of occupational exposure to vibration were insufficient.

Basic demographic information was obtained for all patients and included age, sex, duration of exposure to vibration, and onset of RP. This study was approved by the Institutional Review Board for Human Research, Konkuk University Medical Center (KUH Number 1010816).

Hand perfusion scintigraphy

A low-energy high-resolution single-head gamma camera (E.cam, Siemens Healthcare, Erlangen, Germany) was used to obtain hand perfusion scintigraphy images. The patients immersed one of their hands in cold water (4°C) for 5 min. After 15 minutes of recovery, both hands were placed on the gamma camera detector, with the patient seated. Technetium-99m hydroxymethylene disphosphonate (^{99m}Tc-HDP, 370 MBq) was administered via an upper extremity vein in the side contralateral to the chilled hand or in the dorsal foot vein. Blood flow images were obtained at a rate of 1 frame/1 second for a total of 60 frames, followed by acquisition of a static blood pool image for 5 minutes.

For quantitative analysis, the workstation software was used to draw regions of interest (ROIs) around all of the fingers with the exception of the thumb and the wrist bilaterally on the summed image of the blood flow and static blood pool image (Fig. 1a). By the ROIs, the time-activity curve of the blood flow images was generated for the fingers and the wrist of both hands. The first peak height of the curve and the initial slope were measured from the time-activity curve (Fig. 1b). The chilled hand-to-ambient hand ratios of the first peak height and the initial slope for the fingers and the wrist were calculated. Using the static blood pool image, the chilled hand-to-ambient hand ratio of the blood pool uptake was calculated for the fingers and the wrist. We analysed three morphologic characteristics after cold stimulation: paradoxically increased or slow progress pattern in time-activity curves and inhomogeneous radioactivity uptake of fingers in the blood pool image (Fig. 2). After cold stimulation, patients with RP show two types of findings on hand perfusion scintigraphy compared to the findings of fingers of the opposite hand not subjected to cold stimulation: (1) decreased perfusion or blood pool activity or (2) increased perfusion or blood pool activity. The latter is called paradoxical reaction of RP. Figure 2A shows the specific paradoxically increased uptake pattern in a patient with RP. When the graph shows a gradual increase without an initial spike, the pattern is called a slow progress pattern. The homogeneity of radioactivity uptake was evaluated in the 4 fingers. Increased or decreased radioactivity uptake in comparison with that in each finger is called inhomogeneous radioactivity uptake. Figure 2B shows the inhomogeneous radioactivity uptake and slow progress pattern in a patient with RP. Images were assessed by experienced nuclear medicine physicians who were blinded to the patients' clinical information.

Statistical analysis

Statistical analyses were performed using the SPSS software package for Windows v. 23.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation. Chi-square test, Kruskal-Wallis test, Mann-Whitney U-test, and t-test were performed, as appropriate. Results were considered statistically significant if the p-value was <0.05.

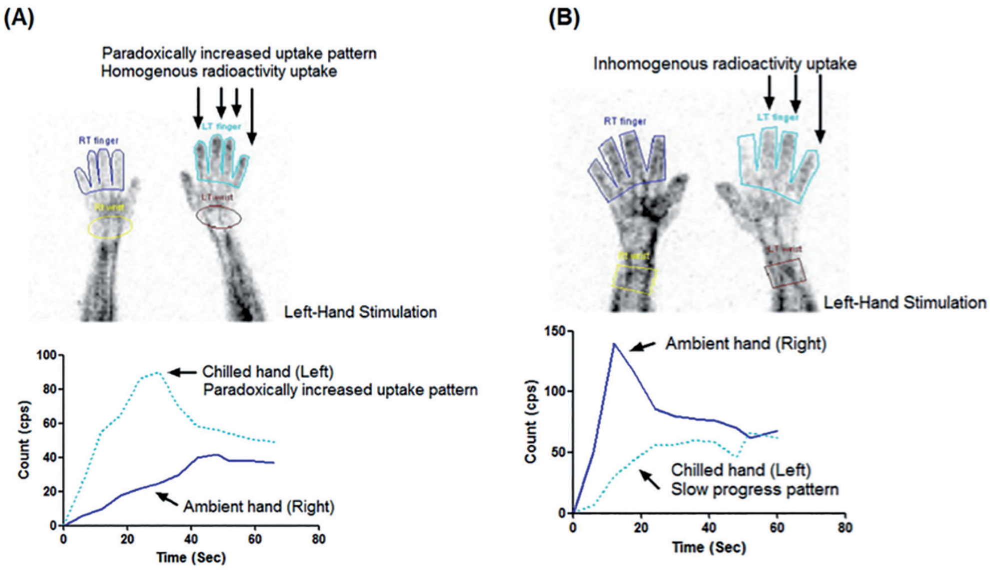

Fig. 2. Hand perfusion scintigraphic characteristics with one hand chilled in a patient with Raynaud's phenomenon. (**A**) The representative image shows the homogenous radioactivity uptake and paradoxically increased blood pool activity in the left second to fifth fingers after cold stimulation. The time activity curve also shows the paradoxically increased uptake pattern compared with the fingers of the opposite hand not undergoing cold stimulation. (**B**) The representative image shows the inhomogeneous radioactivity uptake in the left third to fifth fingers after cold stimulation. The left fingers had decreased blood pool activity compared with the opposite fingers of the hand not undergoing cold stimulation. The time-activity curve shows the slow progress pattern without the initial spike in the chilled hand.

Results

Clinical characteristics

The study included 143 patients divided into three groups: primary RP (n=57), HAVS-related RP (n=71), and SSc-related secondary RP (n=15). Demographic and clinical characteristics are shown in Table I. All 71 patients with HAVS-related RP were mine workers and were exposed to hand-arm vibrations from pneumatic hammers and grinders. The onset of RP after exposure to vibrations was 21.7±7.3 years, with 26.3±7.0 years of vibration exposure time. Sixty-four miners (90.1%) developed RP while they were still working, while the remainder (9.9%) recognised RP after 11.4±8.5 years of retirement. A proportion of the miners suffered from neuropathies which included carpal tunnel syndrome (n=23, 32.4%), peripheral polyneuropathy (n=5, 7.0%), and ulnar neuropathy (n=2, 2.8%). Neuropathy was diagnosed on the basis of nerve conduction studies and subjective symptoms.

Table I. Demographic characteristics of patients with RP.

Characteristics	HAVS (n=71)	Primary RP (n=57)	SSc (n=15)	*p*-value
Age (years)	65.2 ± 5.4 (54-81)	47.1 ± 17.0 (17-77)	51.5 ± 8.4 (35-65)	< 0.001†
Duration of RP (years)	11.4 ± 8.5	3.1 ± 5.1	3.9 ± 3.9	< 0.001†
Male/Female (% of male)	71/71 (100.0)	26/31 (45.6)	2/15(13.3)	< 0.001‡

Data presented as mean ± standard deviation (range). HAVS: hand-arm vibration syndrome; RP: Raynaud's phenomenon; SSc: systemic sclerosis. †HAVS >other groups (p<0.001) on the basis of Kruskal-Wallis test. ‡HAVS >other groups (p<0.001), Primary > SSc (p=0.022) on the basis of Chi-square test.

Table II. Comparison of the 6 quantitative variables of patients with Raynaud's phenomenon.

Parameter		HAVS	Primary RP	SSc	*p*-value
First peak height ratio	Hand	0.90 ± 0.89	1.50 ± 1.50	0.62 ± 0.56	0.013§
	Wrist	0.72 ± 0.31	0.87 ± 0.57	0.70 ± 0.38	0.398
Initial slope ratio	Hand	0.75 ± 0.63	1.43 ± 1.26	0.63 ± 0.57	0.007¶
	Wrist	0.87 ± 0.83	0.87 ± 0.71	0.72 ± 0.43	0.942
Blood pool uptake ratio	Hand	0.85 ± 0.39	1.10 ± 0.72	0.60 ± 0.18	0.002*
	Wrist	0.72 ± 0.18	0.73 ± 0.40	0.68 ± 0.05	0.155

Significant value (p<0.05) are presented in bold.
Data are presented as mean ± standard deviation. HAVS: hand-arm vibration syndrome; RP: Raynaud's phenomenon; SSc: systemic sclerosis. §Primary > HAVS (p=0.009), Primary > SSc (p=0.007). ¶Primary > HAVS (p<0.001), Primary > SSc (p=0.017). *Primary > HAVS (p=0.021), Primary > SSc (p=0.001), HAVS > SSc (p=0.003).

Comparison of quantitative measurements of hand perfusion scintigraphy in patients with RP

The chilled to ambient hand ratios of the first peak height, the initial slope, and blood pool uptake were significantly higher in patients with primary RP than in those with HAVS (p=0.009, p<0.001 and p=0.021, respectively) and SSc related RP (p=0.007, p=0.017 and p=0.001, respectively). The chilled to ambient hand ratio of the blood pool uptake was higher in patients with HAVS than in those with SSc (p=0.003). There was no significant difference in ambient hand ratios of the first peak height and the initial slope between patients with HAVS and those with SSc (p=0.061 and p=0.156, respectively). The three quantitative ratios of the wrist did not differ significantly among the three groups (Table II).

Comparison of pattern of hand perfusion scintigraphy in patients with RP

The presence of paradoxically increased uptake pattern on hand scintigraphy was significantly lower in patients with HAVS and SSc than in those with primary RP (p=0.004 and p=0.030, respectively). The low progression and inhomogeneous radioactivity uptake pattern did not differ among the three cohorts (Table III).

Table III. Comparison of presence of the 3 scintigraphic characteristics in the chilled hand of the patients.

Characteristics	HAVS (n=71)	Primary RP (n=57)	SSc (n=15)	*p*-value
Slow progression pattern	61 (86.0)	51 (89.5)	14 (93.3)	0.664
In-homogenous radio-activity uptake pattern	17 (24.0)	18 (31.6)	4 (26.7)	0.627
Paradoxically increased uptake pattern	15 (19.7)	27 (43.9)	2 (13.3)	0.004†

Significant value ($p<0.05$) are presented in bold.
Data are presented as number (%). HAVS: hand-arm vibration syndrome; RP: Raynaud's phenomenon; SSc: systemic sclerosis. †Primary > HAVS ($p=0.004$), Primary > SSc ($p=0.030$).

Discussion

Raynaud's phenomenon is a prominent manifestation of hand-arm vibration syndrome. We found significant differences in the hand perfusion scintigraphic features between primary RP and HAVS related RP. While the pathophysiological mechanisms of RP associated with prolonged use of vibrating tools are complicated and still unclear, possible explanations include local vascular damage, neural abnormalities, and defects in vascular repair. RP is characterised by decreases in vasoactive substances such as nitric oxide, endothelial nitric oxide synthase, prostacyclin, and increases in endothelin-I, all of which may result in vasoconstriction. In addition, prolonged exposure to vibration increases oxidative activity, sensitivity to alpha2C-adrenoreceptor-mediated vasoconstriction, and results in a generalised increase in sympathetic tone. These changes could contribute to defects in vascular repair and subsequent vasospasm. The concept of intravascular and circulating factors including elevated plasma levels of thrombomodulin, von Willebrand factor, fibronectin, and intercellular adhesion molecule have also been implicated in the pathophysiology of HAVS related RP and may contribute to endothelial injury (4, 15, 16).

On account of the high prevalence of HAVS in various occupations and the medico-legal consequences of this diagnosis, there has been renewed interest in accurately diagnosing the condition (17, 18). Until recently, RP was diagnosed based on a patient's clinical history of characteristic colour changes in the digits provoked by cold or vibration. However, there has been increased focus on the development of objective assessment methods with standardised cut-off values (8, 10, 11, 19, 20). However, the few studies conducted to date that have evaluated the cut-off values for scintigraphic measurements did so without taking into account disease aetiology (10, 12). Owing to insufficient evidence, consensus on the cut-off values for confirmation of HAVS related RP is lacking.

We analysed the 3 morphologic features and 6 quantitative variables of hand perfusion scintigraphy in patients with RP. The morphologic characteristics of scintigraphy that are consistent with the recovery pattern of vasospasm include a slow progress pattern and inhomogeneous radioactivity uptake. The initial spike reflects the recovery phase of RP, since the isotopes start to circulate rapidly after restoration from the vasospasm. On the other hand, a slow progress pattern indicates the pre-recovery phase of RP, due to the stopped flow of isotopes before recovery from the vasospasm. The inhomogeneous radioactivity curve reflects a state of severe heterogeneous vasoconstriction in each digit and vessel (10, 21). The structural changes of the vessel after cold exposure could lead to paradoxical vessel dilatation, which in turn causes a paradoxically increased uptake pattern on hand perfusion scintigraphy (22). There are few well-established definitions of the quantitative measurements of hand perfusion scintigraphic findings. The ratios of blood pool uptake, first peak height, and initial slope ratio may reflect the proportion and discrepancy of the amount of blood flow, but these definitions are open to debate.

To our knowledge, this was the first study to evaluate scintigraphic differences among HAVS-related RP, primary RP, and SSc-related RP. We demonstrated the presence of a significant difference in the chilled to ambient hand ratios of the first peak height, the initial slope, and the blood pool uptake as well as a paradoxically increased uptake pattern in the HAVS and SSc-related RP groups compared to the primary RP group. The different patterns could be explained by the fact that primary and secondary RP may be caused by different mechanisms or involve different vascular changes. This explanation is supported by the fact that while no structural abnormalities or subtle alterations occur in primary RP, secondary RP is more commonly characterised by intravascular alterations, and functional and structural vessel changes compared to primary RP. Definite vascular structural changes and intravascular alterations in secondary RP may be reflected in the results obtained on hand perfusion scintigraphy. Furthermore, we supposed that relatively long-standing exposure to vibration could affect the more severe alterations of vascular structure and functions, as well as ability of reversible dilatation in HAVS, compared to primary RP. These changes may contribute not only to the lower ratios of the first peak height and initial slope, but also to the decreased paradoxical uptake pattern. In comparison with HAVS related RP, SSc-related RP presented with significantly lower chilled to ambient hand ratios of blood pool uptake. The chilled to ambient hand ratios of first peak height were not significantly different ($p=0.061$), but were lower in SSc-related RP than in HAVS-related RP. An intensified vasoconstriction could be related to increased levels of endothelin-1 (ET1). ET-1 induced vasoconstriction is enhanced whenever endothelial structural changes or inflammation occurs. However, ET-1 induced vasoconstriction is minimal when endothelial integrity is preserved, as in HAVS. Indeed, there is some evidence that autoantibodies such as ANA, anti Scl-70, and anticentromere might contribute to vessel structural alternations though induction of endothelial apoptosis, and release of chemokines and cytokines (4). The lower ratios of blood pool uptake and first peak height in SSc-related RP compared to HAVS-related RP could reflect these different disease mechanisms. Further prospective studies are warranted in order to reveal the complex mechanism of each type of RP and to account for the different scintigraphic findings.

In clinical practice, distinguishing primary RP from secondary RP could be challenging, because no single confirmative test exists. Nailfold capillaroscopy is a method most commonly used in clinical practice to identify underlying secondary diseases. This is a non-invasive, inexpensive, and safe imaging tool used in morphological analysis of capillaries in the nailfold area. The presence of capillary dilatation and an area of avascularity suggest an underlying rheumatic condition or predict development of such disease. However, this technique relies on the presence of an experienced clinician capable of differentiating between non-specific findings and abnormal findings. In RP secondary to non-rheumatic diseases, the capillaroscopic image could be normal or non-specific (23). Other tools used to assess the vascular responses in the digits and skin include infrared thermography (IRT) and laser speckle contrast imaging (LSCI). IRT with cold provocation has been proposed as a simple method of measuring the abnormal vascular response in patients with primary and secondary RP. LSCI has excellent reproducibility and allows real time monitoring of peripheral blood perfusion on a large area of the body (24, 25). A difference of >1°C between the fingertips and the dorsum of the hand identified on IRT can help to distinguish primary RP from SSc-related RP (26). In contrast, a recent study showed convincing results than IRT as well as LSCI could not differentiate between primary RP and SSc-related RP (11). In the present study, we confirmed the potential of hand perfusion scintigraphy to distinguish secondary RP including HAVS and SSc from primary RP. A large-scale prospective multicentre study is needed to confirm these results.

It is also important to note that patients with HAVS have significantly longer duration of RP compared to those with primary and CTD-related RP. Although various studies on HAVS and its health effects have been reviewed, public ignorance of the seriousness and irreversibility of HAVS, as well as insufficient HAVS awareness by physicians and a lack of accurate objective methods for early diagnosis may contribute to delayed diagnosis (27). In practice, the same cut-off values for digital blood flow scintigraphy have been applied to the diagnosis of HAVS-related RP and primary RP. Standardisation of separate cut-off values for hand perfusion scintigraphy in HAVS-related RP could establish more accurate diagnostic criteria for HAVS and may even curtail the medico-legal problems associated with this condition.

Our study has several limitations. First, the study was retrospective and cross-sectional, and clinical data were obtained following chart reviews. Since we excluded cases with incomplete or ambiguous descriptions, there is a possibility of some selection bias. The statistical power was limited by the small sample size of patients with systemic sclerosis. Furthermore, it is known that current smoking status is associated with an increased risk of RP in men (28). However, owing to insufficient data regarding smoking history available in the retrospective chart review, we could not evaluate the smoking variables that contribute to RP risk. Finally, we did not measure disease severity by using indexes such as the Stockholm workshop scale and daily exposure duration to vibration. A proposed core set of outcome measures for studying included patient self–reported and physician global assessment, RP attack frequency, and duration (29). A key limiting factor for assessing efficacy in therapeutic studies of RP is the lack of validated objective outcome methods for the evaluation of digital vascular function. For example, one recent study showed infrared thermometry failed to determine the severity of HAVS-related RP (19). Hand perfusion scintigraphy is an object method that could visualise and quantify the peripheral blood flow impairment. A further study is needed to reveal the association between the severity of RP and findings on hand perfusion scintigraphy.

In conclusion, the present study showed a different pattern of hand perfusion scintigraphic findings between HAVS and primary RP, and this difference was statistically significant. These findings suggest that the underlying pathophysiology of diseases may differ, and thus different criteria might be applied when evaluating each case of RP.

References

1. SAUNI R, TOIVIO P, PAAKKONEN R, MALMSTROM J, UITTI J: Work disability after diagnosis of hand-arm vibration syndrome. *Int Arch Occup Environ Health* 2015; 88: 1061-8.
2. GERHARDSSON L, HAGBERG M: Work ability in vibration-exposed workers. *Occup Med* (London) 2014; 64: 629-34.
3. HOUSE R, WILLS M, LISS G, SWITZER-MCINTYRE S, LANDER L, JIANG D: The effect of hand-arm vibration syndrome on quality of life. *Occup Med* (Oxford) 2014; 64: 133-5.
4. PALMER KT, BOVENZI M: Rheumatic effects of vibration at work. *Best Pract Res Clin Rheumatol* 2015; 29: 424-39.
5. LINNEMANN B, ERBE M: Raynauds phenomenon - assessment and differential diagnoses. *VASA* 2015; 44: 166-77.
6. POPE J: Raynaud's phenomenon (primary). *BMJ Clin Evid* 2013; 2013: 1119.
7. THOELEN K, MAIERS K, BONDI KA, COVINO J: Recognizing and treating Raynaud phenomenon. *JAAPA* 2015; 28: 40-4.
8. COUGHLIN PA, CHETTER IC, KENT PJ, KESTER RC: The analysis of sensitivity, specificity, positive predictive value and negative predictive value of cold provocation thermography in the objective diagnosis of the hand-arm vibration syndrome. *Occup Med* (Oxford) 2001; 51: 75-80.
9. SCHMIDT WA, KRAUSE A, SCHICKE B, WERNICKE D: Color Doppler ultrasonography of hand and finger arteries to differentiate primary from secondary forms of Raynaud's phenomenon. *J Rheumatol* 2008; 35: 1591-8.
10. KWON SR, LIM MJ, PARK SG, HYUN IY, PARK W: Diagnosis of Raynaud's phenomenon by (99m)Tc-hydroxymethylene diphosphonate digital blood flow scintigraphy after one-hand chilling. *J Rheumatol* 2009; 36: 1663-70.
11. PAULING JD, SHIPLEY JA, HART DJ, MCGROGAN A, MCHUGH NJ: Use of Laser Speckle Contrast Imaging to Assess Digital Microvascular Function in Primary Raynaud Phenomenon and Systemic Sclerosis: A Comparison Using the Raynaud Condition Score Diary. *J Rheumatol* 2015; 42: 1163-8.
12. LEE JW, JEONG WS, LEE SM, KIM J: Comparison of the diagnostic performances of two protocols of hand perfusion scintigraphy for Raynaud's phenomenon. *Nucl Med Commun* 2012; 33: 1032-8.
13. MAVERAKIS E, PATEL F, KRONENBERG DG *et al.*: International consensus criteria for the

diagnosis of Raynaud's phenomenon. *J Autoimmun* 2014; 48-49: 60-5.
14. VAN DEN HOOGEN F, KHANNA D, FRANSEN J *et al.*: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737-47.
15. WANG YJ, HUANG XL, YAN JW *et al.*: The association between vibration and vascular injury in rheumatic diseases: a review of the literature. *Autoimmunity* 2015; 48: 61-8.
16. MATOBA T: Human response to vibration stress in Japanese workers: lessons from our 35-year studies A narrative review. *Ind Health* 2015; 53: 522-32.
17. YOUAKIM S: The compensation experience of hand-arm vibration syndrome in British Columbia. *Occup Med* (Oxford) 2012; 62: 444-7.
18. LAWSON IJ, MCGEOCH KL: A medical assessment process for a large volume of medico-legal compensation claims for hand-arm vibration syndrome. *Occup Med* (Oxford) 2003; 53: 302-8.
19. YOUAKIM S: Infrared thermometry in the diagnosis of hand-arm vibration syndrome. *Occup Med* (Oxford) 2010; 60: 225-30.
20. CHERKAS LF, CARTER L, SPECTOR TD, HOWELL KJ, BLACK CM, MACGREGOR AJ: Use of thermographic criteria to identify Raynaud's phenomenon in a population setting. *J Rheumatol* 2003; 30: 720-2.
21. PORTER JM, SNIDER RL, BARDANA EJ, ROSCH J, EIDEMILLER LR: The diagnosis and treatment of Raynaud's phenomenon. *Surgery* 1975; 77: 11-23.
22. CHONG A, HA JM, SONG HC, KIM J, CHOI SJ: Conversion to Paradoxical Finding on Technetium-99m-labeled RBC Scintigraphy after Treatment for Secondary Raynaud's Phenomenon. *Nucl Med Mol Imaging* 2013; 47: 278-80.
23. ETEHAD TAVAKOL M, FATEMI A, KARBALAIE A, EMRANI Z, ERLANDSSON BE: Nailfold Capillaroscopy in Rheumatic Diseases: Which Parameters Should Be Evaluated? *Biomed Res Int* 2015; 2015: 974530.
24. RUARO B, SULLI A, ALESSANDRI E, PIZZORNI C, FERRARI G, CUTOLO M: Laser speckle contrast analysis: a new method to evaluate peripheral blood perfusion in systemic sclerosis patients. *Ann Rheum Dis* 2014; 73: 1181-5.
25. ROUSTIT M, MILLET C, BLAISE S, DUFOURNET B, CRACOWSKI JL: Excellent reproducibility of laser speckle contrast imaging to assess skin microvascular reactivity. *Microvasc Res* 2010; 80: 505-11.
26. ANDERSON ME, MOORE TL, LUNT M, HERRICK AL: The 'distal-dorsal difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. *Rheumatology* (Oxford) 2007; 46: 533-8.
27. BODLEY T, NURMOHAMED S, HOLNESS DL, HOUSE R, THOMPSON AM: Health-care barriers for workers with HAVS in Ontario, Canada. *Occup Med* (Oxford) 2015; 65: 154-6.
28. SUTER LG, MURABITO JM, FELSON DT, FRAENKEL L: Smoking, alcohol consumption, and Raynaud's phenomenon in middle age. *Am J Med* 2007; 120: 264-71.
29. MERKEL PA, HERLYN K, MARTIN RW *et al.*: Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002; 46: 2410-20.