Laser Doppler Imaging of Skin Blood Flow for Assessing Peripheral Vascular Impairment in Hand-Arm Vibration Syndrome

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Abstract: The objective of this study was to evaluate the usefulness of laser Doppler imaging (LDPI) of the skin blood flow for assessing peripheral vascular impairment in the hand-arm vibration syndrome (HA VS). The subjects were 46 male patients with HA VS, aged 50 to 69 yr, and 31 healthy male volunteers of similar age as controls. A cold provocation test was carried out by immersing a subject’s hand on his more severely affected side into cold water at a temperature of 10°C for 10 min. Repeated image scanning of skin blood flow of the index, middle, and ring fingers was performed every 2 min before, during, and after the cold water immersion using a PMI-II laser Doppler perfusion imager. The mean blood perfusion values in the distal phalanx area of the fingers were calculated on each image. The patients suffering from vibration-induced white finger (VWF, n=20) demonstrated significantly lower skin blood perfusion at each interval of the test as compared with those without VWF (n=26) and the controls (p<0.01, ANOVA). The blood perfusions in the HA VS patients were associated with the severity of the symptoms as classified by the Stockholm Workshop scale for vascular staging. When a subject was considered to be positive if any of the tested fingers showing a decreased blood perfusion and/or a delayed recovery pattern, the sensitivity was 80.0%, and the specificity was 84.6% and 93.5% for patients without VWF and the controls, respectively. These results suggest that the LDPI technique could provide detailed and accurate information that may help detect the existence of impaired vascular regulation to cold exposure in the fingers of workers exposed to hand-transmitted vibration.

Key words: Hand-arm vibration, Vibration-induced white finger, Finger skin blood flow, Laser Doppler perfusion imaging, Cold provocation test

Introduction

Long-term exposure to hand-transmitted vibration at work can be the cause of various symptoms, such as the evolution of early sensory neural disorders with paraesthesias and pain gradually becoming persistent, and increasing motor neural and musculoskeletal symptoms in the hands and arms (hand-arm vibration syndrome: HAVS)1-3). Vibration-induced white finger (VWF), the secondary Raynaud’s phenomenon, is the main clinical manifestation of HAVS and is characterized by asymmetrical intermittent reversible vasospasms of the digital arteries. The vasospastic abnormalities include the components of an enhanced vasoconstriction and impaired vasodilatation of the digital arteries provoked by a cold
environment. Several physiological tests in combination with local cooling of the hands or fingers have been used in the diagnosis of HAVS and the grading of its severity. Laser Doppler velocimetry is one of the noninvasive methods for the measurement of finger blood flow to surface tissue. The technique can be used to investigate the response to a vasoconstrictive stimulus, such as cold water immersion, and has been used with some workers who use hand-held vibrating tools. Laser Doppler perfusion imaging (LDPI) is a new technique employing a two-dimensional horizontal scanning of the blood flow in a specific tissue without the necessity for surface contact. By the introduction of the imaging concept, the spatial heterogeneity of the cutaneous tissue perfusion can be investigated, while, at the same time, averaging the blood perfusion over an area of a specific extension increases the reproducibility. The LDPI technique may therefore have the benefit of detecting vasospastic abnormalities of the digital artery in HAVS patients, which generally appear with an inhomogeneous reaction to cold.

In the present study, measurements of the changes in finger skin blood flow in response to a cold water immersion test were performed in patients suffering from HAVS and unexposed healthy controls by using LDPI in order to examine whether the technique can provide valuable information that may support the diagnosis of the peripheral vascular impairment of workers occupationally exposed to hand-arm vibration.

Subjects and Methods

Subjects

The present subjects examined were 46 male patients, aged 50 to 69 yr, with HAVS and 31 healthy male volunteers of similar age as controls. The mean (SD) age of the patients and the controls was 61.2 (4.8) yr and 60.3 (4.9) yr, respectively, and did not differ significantly. All subjects were unaffected by diabetes mellitus, cerebral vascular disease, or heart disease. Of them 12 patients and 7 controls were treated for hypertension, but none of them took any vasoactive medication at the time of examination. All patients were treated for hypertension, but none of them took any vasoactive medication at the time of examination. The patients were under treatments and had been employed as operators of rock drills, vibrators, pick hummers for tunneling, mining, and construction (n=28), and chain saws and bush cutters in forestry (n=18). Their means for yrs of vibration exposure and yrs under treatment were 31.5 (8.1) and 2.4 (1.6), respectively.

Of the HAVS patients, 20 suffered from VWF symptoms, and all subjects complained of sensorineural disturbances in the fingers and hands, such as numbness, tingling, damaged cutaneous perception, or impaired manipulative dexterity. According to the Stockholm Workshop scale (SWS), 5 subjects classified in the stage of 1V, 8 in 2V, 7 in 3V, and 26 in 0V for vascular staging, and 13 subjects were recognized to be in the stage of 3SN, 25 in 2SN, and 8 in 1SN for sensorineural staging. The control subjects were office workers, manufacturers, car drivers, farmers, and medical service employees. None of them operated hand-held vibrating tools habitually in their routine work or had any sign or symptoms consistent with the primary Raynaud’s phenomenon.

The subjects signed a written informed consent form after receiving a detailed explanation of the study aims and procedures. The protocol of this study was approved by the Ethics Committee of the Wakayama Medical University.

Laser Doppler perfusion imaging

The examinations were performed in a quiet, climatized room (24.2 ± 0.4°C) after the subjects had sufficient rest for equilibration to room temperature. They were asked to abstain from smoking and drinking beverages with caffeine and alcohol and to fast for at least 2 h before the examinations. A cold provocation test was conducted by well-trained examiners who had sufficient knowledge of technical aspects and risk of the test under the supervision of a medical doctor. Prior to the test, blood pressure measurements were performed to identify the presence of severe hypertension which might cause either elevated arterial pressure or vasogenic shock due to excessive response to cold stress. The subjects who were approved by the medical doctor underwent the cold test and they could stop the test at any time on request. The subjects immersed the hand of more severely affected side into a cold water bath at a temperature of 10°C for 10 min. Repeated two-dimensional image scanning of skin blood perfusion of the fingers was performed at 2-min intervals before, during, and after the cold-water hand immersion using the laser Doppler perfusion imager (Periscan PIM-II, PERIMED Co., Sweden). The distance between the tissue surface and the lower part of the scanner head during image capturing was fixed to 15 cm. With the system resolution set on low and the image size at 45 × 45 pixels, a 10 × 10 cm tissue area at the palmar side of the hand including the index, middle, and ring fingers was illuminated during the period of about 50 s per each scanning. When capturing perfusion images, the ambient light level was kept at a minimum in order to avoid the influence on the laser light and the recorded perfusion signals. The immersed hand was gently wiped dry immediately after the
end of the immersion period.

The low power (1 mW) laser beam (wavelength, 670 nm) successively scanned the tissue by point-by-point irradiation (Fig. 1). In the tissue, the light was scattered, and the frequency shifted as it interacted with the moving blood cells according to the Doppler principle. A fraction of the back-scattered light reached a photo-detector in the scanner head by which the light was demodulated and converted into an electrical signal. The signal was further processed to scale linearly with tissue perfusion defined as the product of the blood cell velocity and concentration. All perfusion signals were eventually combined to form a color-coded image representing the spatial variability of the skin perfusion. A numerical perfusion reading was also obtained for each measurement site in terms of the voltage (V). In the present analysis, the averages of the blood perfusion in the distal phalanx area of the tested fingers were calculated on each of 13 images (3, 5, and 5 images for before, during, and after the cold provocation) obtained in the course of the observation. We preliminarily tested the reproducibility of the LDPI method in 5 healthy male volunteers aged 28 to 35 yr. The mapping of the perfusion was repeated 10 times at 1-min intervals on the palm of the fingertip before and during the hand was immersed in water at 5 cm in depth. The water temperature was adjusted individually to correspond to mean skin temperature of the whole hand measured by non-contact thermography. As the results, the average of coefficient of variation before and during the hand immersion was 3.3% (range, 2.6 to 3.9%) and 3.6% (range, 3.0 to 4.6%), respectively.

**Data analysis**

To compare the cold response of the skin blood perfusion between groups, a single summary measure of the perfusion readings at the baseline, cooling, and recovery phases of the cold test was calculated as follows: the median of three pre-cooling readings obtained within 5 min (baseline), the average of three readings during the last 5 min of the cold water immersion (cooling), and the average of five readings within 10 min of the removal of the hand from the cold water (recovery). In addition to these representative variables, to obtain a numerical expression of the increase in blood perfusions following cold provocation, we determined a “recovery ratio index” by dividing the average value during the recovery phase by the lowest value during the cooling phase.

Analysis of variance (ANOVA) followed by the Bonferroni correction for multiple comparisons was used to test the difference in the averages of the variables between groups. The sensitivity and specificity of several blood perfusion parameters for the detection of VWF-positive were calculated with standard formulas. The results are expressed as the mean (SD), number of subjects, and percentages. The level of significance was defined as p<0.05. All statistical analyses were conducted using the SPSS statistical package 12.0 for Windows (SPSS Software, Inc., Chicago, IL).

**Results**

The relative changes in laser Doppler perfusion images of the tested three fingers of representative examples from the HAVS patients and controls are shown in Fig. 2. The HAVS patients were divided according to whether the subject was symptomatic of VWF or not. At each image, the skin blood perfusion was color-coded using a scale ranging from a dark blue (lowest value) to red (highest value). The difference in the responses of skin blood perfusion under the condition of cold provocation between VWF patients and the other groups was clearly demonstrated in these sequences of images.

Figure 3 summarizes the changes in the skin blood perfusion of the middle finger during the cold water immersion test among three subgroups of subjects. Prior to cooling, the blood perfusions of the patients with VWF were lower than those of patients without VWF and the controls. When the hand was immersed in cold water, the blood perfusions in all subjects decreased sharply during the first few minutes of immersion. Among patients without VWF and the controls, the blood perfusions increased slightly and were then stable at a constant level during the later phase of immersion. However, those in VWF patients remained at the lowest level that was observed at the first 1 min of the immersion. Furthermore, when the hand was removed from cold water, the blood perfusions in patients without VWF
and the controls recovered rapidly and nearly returned to the baseline level. In the VWF group, there was only a slight increase immediately after the immersion and no recovery by the end of the phase. Throughout the course of the cold water test, the patients with VWF demonstrated significantly lower blood perfusion than those without VWF and the controls at all time points except the beginning of the hand immersion.

Table 1 shows the comparisons of the blood perfusion summary values at each phase of the cold water test between HAVS patients and controls. Significant differences between the patients with VWF and those without VWF and the controls were observed for all of the blood perfusion representative variables. When the HAVS patients were divided according to the SWS for vascular disorders, the blood perfusion variables were almost associated with the progression of the vascular staging. The VWF patients classified into 3V showed the lowest values when compared with those in 1V and 2V with the exception of the baseline values. There was a tendency for the blood perfusion values to be lower in the patients without VWF than in the controls, but significant differences between groups were not observed.

Table 2 shows the accuracy of the LDPI blood perfusion variables to distinguish a hand affected with VWF from one without symptoms. The lower normal limits (cut-off values) discriminating between normal or abnormal results for the blood perfusion variables were tentatively set at values that were calculated as 1.96SD away from the mean values in the controls of this study. The cut-off values were 1.5, 1.0, and 1.2 for the values during baseline, cooling, and recovery phases, respectively, and 1.0 for the recovery ratio index. When the number of hands with finger(s) with values below
the cut-off value was counted separately for each of the variables, the value of the recovery phase showed a higher sensitivity than the other variables, and the number of false-positive cases in the patients without VWF and the controls was the smallest by use of the value of the cooling phase as well as the recovery ratio index. When a subject was considered to be positive if his hand showing abnormal results for any of the four blood perfusion variables, the sensitivity was 80.0%, and the specificity was 84.6% and 93.5% for patients without VWF and the controls, respectively. Additionally, if considering only the VWF patients staged at 2V or 3V of SWS (moderate or severe cases) in the analysis, the sensitivity for VWF-positive increased to 86.7%. The positive and negative predictive values calculated in the HAVS patients were 80.0% and 84.6%, respectively.

**Discussion**

The objective of this study was to examine the potential of blood flow monitoring by LDPI during a cold water immersion test in HA v syndrome patients and controls. The table below shows the accuracy of the LDPI blood perfusion variables for the diagnosis of vibration-induced white finger.

<table>
<thead>
<tr>
<th>Evaluation for LDPI blood perfusion variables</th>
<th>Blood perfusion value (V)</th>
<th>Recovery ratio index</th>
<th>Result of the LDPI test&lt;sup&gt;d&lt;/sup&gt;</th>
<th>n</th>
<th>Sn/Sp&lt;sup&gt;e&lt;/sup&gt;</th>
<th>PPV/NPV&lt;sup&gt;f&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Baseline (&lt;1.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cooling (&lt;1.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Recovery (&lt;1.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Recovery ratio index (&lt;1.0)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>HA VWF (+)</td>
<td>N=20</td>
<td>8</td>
<td>40.0</td>
<td>9</td>
<td>45.0</td>
<td>15</td>
</tr>
<tr>
<td>HA VWF (−)</td>
<td>N=26</td>
<td>4</td>
<td>15.4</td>
<td>2</td>
<td>7.7</td>
<td>4</td>
</tr>
<tr>
<td>Controls</td>
<td>N=31</td>
<td>1</td>
<td>3.2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are means (SD). *p<0.05, **p<0.01 versus controls, ′p<0.05, ′′p<0.01 versus patients without VWF.
<sup>a</sup>Staged according to the Stockholm Workshop scale.
<sup>b</sup>The mean (SD) age of the patients with VWF and those without VWF was 62.2 (4.9) yr and 60.3 (4.8) yr, respectively.
<sup>c</sup>Cut-off values for the LDPI variables were defined as <1.96SD away from the mean values in the controls.
<sup>d</sup>The number of positive subjects that were counted separately for each of the LDPI variables.
<sup>e</sup>Positive when any of the index, middle, and ring fingers showed values below the cut-off values.
<sup>f</sup>Positive when subject had the hand with finger(s) showing abnormal results for any of the four LDPI variables.
<sup>Sn</sup>, sensitivity; <sup>Sp</sup>, specificity; PPV, positive predictive value; NPV, negative predictive value (%).
immersion test as an objective diagnostic examination of the vascular disturbance of HAVS. We demonstrated that finger blood perfusions at all time phases of the cold test of VWF patients were significantly lower than those of patients without VWF and the controls. The LDPI method using several blood perfusion variables as the detection parameters could provide a clinically acceptable diagnostic accuracy for determining the presence or absence of VWF. The technique may be useful for investigating the response of digital arterial vessels to a cold stimulus and, therefore, provide important data that could help detect the peripheral vascular impairment in workers exposed to hand-arm vibration.

A number of quantitative physiological tests have been developed to detect circulatory impairment in the fingers of vibration-exposed workers\(^5\). Laser Doppler flowmetry, which is based on recording the Doppler shifts that photons undergo when scattered in moving blood cells, allows continuous and noninvasive recording of cutaneous tissue blood perfusion\(^7,8\). The method has already contributed to the investigation of the digital vascular abnormalities in HAVS and to an understanding of their pathogenesis\(^9,10\). However, with an increasing number of applications, a low spatial resolution (less than 1 mm) was revealed to be one of the most severe limitations of the technique because cutaneous circulation is known to be heterogeneous, resulting in significant differences in the perfusion values, even at adjacent sites\(^11,12\). The LDPI technique is another method used to measure the skin blood flow to surface tissue. It is based on the dynamic scattering of coherent light in tissue for mapping blood perfusion over a specific area\(^13,14\). The main advantage of this technique is that blood flow is measured over an area rather than at a single site, obviating some of the difficulties with spatial variability inherent in the signal-probe technique\(^13,14\). It has been shown that the digital vasospastic reaction to cold should be evaluated with several fingers of the hand because, particularly in the secondary Raynaud’s phenomenon, individual fingers are expected to exhibit an inhomogeneous reaction to cold exposure\(^3–5\). The LDPI technique is considered to be suitable for this purpose and can provide an objective assessment of vascular reactivity in the finger arteries of vibration-exposed workers. Furthermore, the laser beam is non-contact, as opposed to the single probe, which involves direct contact with the skin and which could, through this contact, influence the blood flow via pressure and movement artefacts\(^20\).

In the present study, the LDPI method demonstrated that there is a more intense cooling reaction and a significantly delayed recovery after cold provocation in VWF patients than in those without VWF and the controls. The blood perfusion of the subjects without VWF gradually increased during the cold water immersion, but that of the VWF patients remained at the very low level observed at the beginning of the immersion. Furthermore, after the end of immersion, the blood perfusion of the subjects without VWF showed a regular increase, while such a recovery pattern could not be found in the VWF patients. Although the pathogenesis of VWF remains unclear, it is proposed that the vascular abnormalities manifest themselves as periodic blanching of the affected fingers, usually provoked by cold. Thus, the clinical condition of VWF may be characterized by an excessive vasospastic response to cold, which include the components of enhanced vasoconstriction and impaired vasodilatation of the digital arteries\(^3–5\). A more extreme sympathetic vasomotor activity in response to cold in VWF subjects can cause stronger vasoconstriction and then reduction in cold-induced vasodilatation, and, thereby, lead to considerably decreased blood perfusion during the later phase of immersion\(^21,22\). The increased vasoconstriction and/or delayed vasodilatation, which produce low opening pressure of the digital arteries, may further contribute to a retarded increase of blood perfusion after the end of hand immersion. The digital vessel abnormalities in finger arteries\(^23\), which are characterized by a medial muscular hypertrophy with narrowed lumen\(^24,25\) and are accompanied by impaired endothelium\(^26,27\), have been shown to be associated with the vasospastic response to cold in VWF patients.

The results of our study have indicated that the LDPI measurement in combination with cold-water hand immersion can be a useful test to differentiate between individuals with and without vascular abnormalities among HAVS patients. The most commonly applied methods in the assessment of abnormal vascular response to cold in HAVS are the measurements of finger skin temperature and finger systolic blood pressure after subjecting fingers or hands to cold exposure. It has been reported that the skin temperature rewarming test may lack the necessary sensitivity and specificity for distinguishing between regular vascular reactivity and cold-induced vasospasm\(^24–30\). The diagnostic value of the finger systolic pressure test can be difficult to define, as there has been a variation in both the nature of the cooling procedure and the outcome parameter used\(^31–33\). However, the technique has been proposed as a useful and reproducible laboratory test for quantifying the degree of vascular disturbance in HAVS\(^34\). The sensitivity and specificity in this study of the LDPI method using a combination of several blood perfusion variables as an
outcome parameter were estimated to be approximately comparable to those provided by a finger systolic pressure test. Furthermore, our results showed that the LDPI technique had high specificity, but its sensitivity tended to be relatively lower, suggesting that the method may be useful in detecting the existence of vascular abnormalities in HAVS but may not be suitable as a screening tool.

The finger skin temperature rewarming test is a measure of the vasodilatory responsiveness of the digital blood vessels after the cold stimulus\(^{30}\). In the LDPI method, the observation of blood perfusion after cold water immersion may essentially evaluate the vasodilatation of finger arteries. The finger temperature test was found to give a wide range of results in normal subjects, although it had some influence in ruling out vascular problems. The overlap of the VWF patients and normal subjects may lead to a higher false-positive ratio and limit the diagnostic value of the test\(^{30}\). In our study, when the diagnostic accuracy was evaluated separately for each of the LDPI blood perfusion variables, there was a tendency for the perfusion values of the recovery phase to have high sensitivity, but its specificity seemed low compared to the other variables. The sampling depth for skin tissue in the LDPI technique is reported to be a few hundred micrometers\(^{36}\), indicating that the technique measures superficial blood flow, which is more closely related to the skin surface temperature than deeply located vessels\(^{9}\). In contrast to the finger temperature test, the finger systolic pressure test may record the interruption of digital blood flow in the context of vasoconstriction\(^{77}\). The LDPI measurement revealed a significantly pronounced reduction of blood perfusion in the fingers of the immersed hand of patients with VWF, which could represent the vasoconstrictive component of the subjects. This result suggests that the method may offer information on both aspects of the vascular reflection to cold, namely, the vasoconstrictive response to cold exposure and that following vasodilatation. In this regards, a number of researchers have reported that the finger systolic pressure test constantly shows high specificity but somewhat lower sensitivity\(^{29, 35, 38}\). Among the blood perfusion variables determined in this study, the false-positive cases appeared to be fewer when the value of the immersion phase was used rather than the other variables. In addition, the results of our study showed that the initial blood perfusion before cold water immersion were able to discriminate on a group basis between those with and without VWF. However, its sensitivity and specificity to distinguish between such individuals were relatively low. Therefore, the assessment of blood flow responses to a cold challenge is needed to confirm the enhanced vasoconstriction

and impaired vasodilatation of the digital arteries that are characteristics of VWF.

There are several potential limitations in this study. The study sample consisted of a relatively small number and may be insufficient to generalize all of the results obtained. In addition to the sample size, although the HAVS patients and controls in this study were selected to eliminate the possible effects of confounders, such as a subject’s age or disease profiles, the pair-matching procedure was not applied for the selection. There are as yet only a few studies applying the LDPI technique to examine the peripheral vascular response to cold stimuli, especially in connection with Raynaud’s phenomenon\(^{16, 30}\). We consider that our testing protocols and Doppler image analysis used in this study are adequate to disclose enhanced vasoconstriction or impaired vasodilatation of the digital arteries of VWF patients. However, these procedures need to be further improved, and the influence of several factors that might be a source of error in the measurements needs to be evaluated. Furthermore, the lower normal limits of the various blood perfusion variables were temporarily determined based on the results in the controls of this study. The values can probably be used for most other populations of workers suffering from vascular symptoms in HAVS, since almost all affected subjects are men of a similar range of age; however, it would be desirable that a future study with use of large number of samples and application of receiver operating characteristics analysis will be carried out to establish the optimum cut-off points that minimize the false positive and negative results.

### Conclusion

The diagnosis of HAVS is essentially based on the presence of cold-induced episodes of white fingers in patients with an occupational history of vibration exposure and no other known causes of the secondary Raynaud’s phenomenon\(^{16}\). There is the need for an accurate objective test for assistance with the diagnosis of this condition and grading of its severity. In contrast to other objective testing tools, the LDPI, which monitors blood flow in a wide range without requiring surface contact, offers the advantage of simultaneous measurement of several fingers of the hand during cold exposure and following recovery period. The LDPI method may be a valid quantitative tool for the study of vasospastic abnormalities of digital arteries to cold in VWF patients and, thereby, useful for identifying the peripheral vascular disturbances of workers exposed to hand-arm vibration.
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