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Review

Review of Different Quantification Methods for the Diagnosis of Digital Vascular Abnormalities in Hand-arm Vibration Syndrome

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Abstract: Review of Different Quantification Methods for the Diagnosis of Digital Vascular Abnormalities in Hand-arm Vibration Syndrome: MH Mahbub, *et al.* Department of Hygiene, Yamaguchi University Graduate School of Medicine—Objective: This study was undertaken to review the diagnostic ability of different quantification methods in the assessment of vibration-induced white finger (VWF), the typical clinical manifestation of vascular injuries in Hand-arm Vibration Syndrome (HAVS). **Methods:** A literature search of original and major review articles related to the quantification techniques for diagnosing vascular injuries in HAVS was performed. Relevant data from the publications were extracted and included in this study for reporting and discussion. **Results:** Few studies were available to substantiate the diagnostic techniques using the nail press test and nailfold capillaroscopy. Also, few studies were found to conclusively demonstrate the diagnostic ability using thermometry and thermography incorporated with cold provocation. Some recent reports raised the question regarding the diagnostic ability of finger plethysmography; but by virtue of its comparable assessment parameters and better diagnostic performance, plethysmography appears to be a suitable diagnostic method. In noninvasive quantification of vascular injuries, diagnostic techniques like laser Doppler perfusion imaging and nailfold capillaroscopy require further evaluation in future studies. **Conclusions:** For a reliable objective diagnosis of VWF at present, quantification of vascular responses using a test battery including established methods like thermometry or thermography and strain gauge plethysmography appears to be useful.

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Prolonged use of vibrating handheld tools results in the development of HAVS, a complex health hazard involving vascular, neural and musculoskeletal systems. VWF, a secondary form of Raynaud's phenomenon (RP), is the typical clinical manifestation of vascular injuries in HAVS. Episodic blanching of the fingers is characteristic for VWF, which is commonly provoked by exposure to cold.

Millions of workers are occupationally exposed to hand-transmitted vibration in the world, and the prevalence of VWF among them can be as high as 71%, depending on the type and duration of exposure to hand-arm vibration[1]. In many industrialized countries, VWF is a common prescribed occupational disease. Among the workers using vibratory tools, the prevalence of VWF varies from 0–5% in tropical countries to 80–100% in workers exposed to high vibration magnitude in northern countries[2]. In the industrialized countries, the costs of awarding compensation claims and disability benefits associated with VWF are very high. At present, to diagnose VWF or HAVS objectively, no gold standard test is available. Also, there is a growing controversy regarding the diagnostic ability of the widely used tests[3]. Currently, for diagnosing VWF, a medical interview by a qualified physician including a positive history of finger blanching attacks in persons occupationally exposed to hand-transmitted vibration is the best method[4]. But to diagnose VWF among such workers, quantitative objective assessment is essential, which should also aid in grading its severity and assessing progression or regression over time.

To quantify and detect digital vascular disorders in vibration-exposed workers, several objective assessment techniques have been described so far. A descriptive review of articles published in English and Japanese was conducted based on the studies including different quantification methods in distinguishing VWF patients

Table 1. Nail press test involving cold immersion for diagnosis of VWF

Author	Year of reference	Evaluation parameter (Prolonged recovery time)	Sensitivity (%)	Specificity[§] (%)
Harada	1987	≥4.5 sec, 5 min after immersion	56.9	92.5
		≥4 sec, 10 min after immersion	53.4	92.5

[§]Specificity is shown for non-vibration-exposed controls.

from controls and the pertinent reports. The purpose of the current review study was to summarize the different quantitative measurement techniques for diagnosing vascular abnormalities in HAVS and their contributions and limitations in the context of recent advances in knowledge.

The Nature of the Vascular Abnormality in HAVS

The exact pathophysiological mechanisms for vascular injury in HAVS are not fully understood yet. Among patients with VWF, hyperreactivity of the sympathetic nervous system is reflected by the presence of high digital vascular tone with lowered skin temperature and blood flow in fingers under cold environments[5–7]. Among the local vasoregulatory components, increased endothelin-1 and plasma catecholamine release with increased α_2-adrenoreceptor reactivity together with inadequate release of nitric oxide and calcitonin gene-related peptide lead to the dysregulation of vascular tone in favor of vasoconstriction[8]. Moreover, several circulating intravascular factors have been implicated in the pathophysiology of vibration-induced vascular injury. These include increased plasma level of thrombomodulin and von Willebrand factor, enhanced erythrocyte aggregation and hypodeformability, platelet activation, increased levels of thromboxane A_2 and intercellular adhesion molecules[8]. All these may be followed by narrowing of the arterial lumen with medial smooth muscle hypertrophy and diminished digital microcirculatory blood flow [3, 7].

Measurement Techniques

To assess digital vascular injuries in HAVS, several measurement techniques including detection of recovery time after nail compression, nailfold capillary microscopy, plethysmography, thermometry and thermography, and laser Doppler imaging and flowmetry have been used. Some of these assess the digital skin microcirculation, while the others assess digital arteries. Nailfold capillary microscopy can assess structural changes in the superficial cutaneous vasculature. Most of these modalities are conducted with measurement of digital vascular responses to cold provocation. Theoretically, the same cold stress should induce greater vasospasm in patients with severe VWF than with milder VWF.

Recovery Time after Nail Compression

So far, a few studies have applied this technique to evaluate subjects exposed to hand-arm vibration. In the nail compression method, the second, third and fourth fingers of the test subject are pressed strongly for 10 sec by the thumb and index finger of the examiner. After releasing the pressure, the recovery time to regain normal color in the nail is evaluated[9].

In a study of Harada, the nail compression test was conducted after immersion of hands into water at 10°C for 10 min[10]. In that study, the nail compression method had a sensitivity of less than 60% and a specificity of around 90% (Table 1).

The nail compression test is simple, safe and inexpensive; but the disadvantage is that the force of compression and the evaluation of recovery time for the nail to regain its color vary according to the examiner's skill and experience. Moreover, the nail compression method has low discriminative power, and the reproducibility of it is also uncertain[11]. All these disadvantages make the usability of this technique limited and not popular in evaluation of VWF.

Nailfold Capillary Microscopy

In the nailfold, capillaries lie parallel to the skin surface, while in other areas, they appear to be perpendicular. Here, the capillaries are easily accessible for morphological evaluation. Nailfold microscopy with direct in vivo inspection of skin capillaries is usually performed by ophthalmoscope, stereomicroscope, wide field photomicrography or video capillaroscopy and computer-based image analysis. The potential of nailfold capillary microscopy has been tested in the quantitative assessment of microcirculatory abnormalities in primary RP and connective tissue diseases. But there are few capillaroscopic reports for VWF, and the diagnostic values for the characteristic abnormalities have not been established for VWF.

In primary RP, the pattern of the nailfold capillaries remains normal. Capillary abnormalities in secondary RP are commonly characterized by decreased capillary density, avascularity, giant or megacapillaries and micro hemorrhages[12]. The most common abnormality in VWF has been reported to be a reduced number of capillary

loops/capillary dropouts [3, 14]. Morphological alterations like tortuosity of the capillary loops and their elongation with disarrangement of capillary polarity (loss of parallel pattern) were also observed among VWF patients, whereas all controls had normal capillary morphology[13]. There is a scarcity of research works on quantification of the capillary pattern in VWF. In the study of Littleford *et al*., the authors suggested a scoring system for assessing microvascular abnormality in VWF[13].

The method of video capillaroscopy allows measurement not only of dimensions of individual capillaries, but also examination of individual red blood cells and their velocity[15]. Therefore, by using this technique, changes in capillary red blood cell velocity resulting from cold provocation can be assessed. Despite some subjective elements in measurements by nailfold capillaroscopy such as visualization and inclusion of capillaries and the appropriate point for measurement of dimensions, it has potential in the quantification of capillary abnormalities in VWF.

Thermometry and Thermography

Measurement of finger skin temperature (FST) reflects indirect assessment of finger blood flow[16]. To measure FST easily and rapidly, contact thermometry or thermography is widely used, both of which are considered to be useful for this purpose. Thermometry and thermography allow simultaneous measurements of all fingers. For thermometry, point transducers like thermocouples or thermistors are placed into contact with the finger skin. There are two types of thermography: contact thermography and infrared thermography. Infrared thermography does not require any contact with the skin. Instead, an infrared camera records the heat radiation from the hands including the entire lengths of fingers.

In evaluating VWF patients, quantification of FST has been incorporated with responses to cold stress or provocation. For the cold provocation test, immersion of the hand/s into water at 12 ± 0.5ºC for 5 min under a room temperature of 21 ± 1ºC following an adaptation period of at least 30 min at that temperature was suggested by ISO 14835-1[16]. On the other hand, for diagnosing VWF, a cold provocation test with immersion of the hand/s in water at 10ºC for 10 min is commonly employed in Japan, for which the normative data have been established by the Research Society for Vibration Syndrome, Japan Society for Occupational Health[17]. Measuring the FST responses to cold provocation is helpful in the diagnosis of VWF and also in the assessment of its reversibility in patients currently not working with handheld vibratory tools[18]. Moreover, FST measurements with cold provocation help to detect subclinical vascular disorders in asymptomatic patients exposed to vibration[19]. In the investigation undertaken by Suizu and Harada, the ISO 14835-1 test method with measurement of FST by thermistors was found repeatable[20]. The reported sensitivity and specificity from several studies involving thermometry[10, 21–29] and thermography[29–31] with a cold water immersion test in distinguishing VWF patients from controls are presented in Table 2, which indicates that the diagnostic ability of FST measurements with cold provocation is inconsistent. In the study of Coughlin *et al*., the researchers investigated the potential of cold provocation thermography with a water temperature of 5°C for 1 min as an objective test to diagnose the digital vasospasm in HAVS patients[31]. They concluded that cold provocation thermography has good sensitivity, specificity, positive predictive value and negative predictive value in clinical diagnosis of HAVS. But another cold provocation thermography study by Poole *et al*. showed low sensitivity and specificity, and the authors concluded that themographic assessment with a cold provocation using water at 15°C for 5 min did not appear to discriminate VWF patients from controls[29].

With thermometry and thermography, various parameters of FST responses during and following cold provocation have been quantified by different researchers. Application of different parameters may lead to different conclusions in the same subject and influence the diagnostic significance of the test results[3].

As the vascular injury in VWF may be finger specific or even phalanx specific, measurements by thermocouple and thermistor may be highly influenced by the measurement site, as such point transducers can only quantify the surrounding blood flow from a limited area. On the other hand, thermography provides important information on temperature distribution over the entire hand and entire lengths of fingers[18]. Therefore, thermography appears to be more effective compared with point transducers in measuring FST. However, point transducers are relatively inexpensive and easy of use, and they can be used during hand immersion in water, which is not possible with thermal imaging devices[32].

The recent controversies regarding the diagnostic ability of the cold stress test appear to be related to the test conditions like the extent and duration of the cold provocation, water temperature and evaluation parameters. However, both thermometry and thermography in combination with cold provocation have been shown to provide useful diagnostic information for VWF.

Laser Doppler Flowmetry

The laser Doppler technique constitutes a useful approach in noninvasive quantification of microvascular blood flow. As suitable tools for measuring the changes in digital skin blood flow, laser Doppler perfusion monitoring (LDPM) and laser Doppler perfusion imaging (LDPI) are widely used. The LDPM is a method of continuous monitoring for microvascular flow by recording the flux of red cells in the path of laser beams from optical fibers carrying the light to and from the tissue; in contrast,

Table 2. Selected studies involving a cold immersion test with FST measurement by thermometry and thermography for diagnosis of VWF

Measurement tool and author (s)	Year of reference	Evaluation parameter	Sensitivity[#] (%)	Specificity[†] (%)
Thermometry				
Juul and Nielsen	1981	Rewarming time to room temperature	100	100
Brubaker *et al*.	1983	Rewarming at 3 min after ischemia for initial 5 min during immersion	72	82
Hack *et al*.	1986	Rewarming at 3 min after ischemia for initial 5 min during immersion	73	74
Harada	1987	FST at 5 and 10 min after immersion	24, 22	95, 98
Pelmear *et al*.	1987	FST at hyperemia and at 10 min during immersion	73, 76	52, 43
Virokannas and Rintamaki	1991	Rewarming rate and rewarming $temperature_{max}$ after immersion	67, 69	70, 68
Bogadi-Sare and Zavalic	1994	Recovery rate <75 and <90% 10 min after immersion	59, 69	81, 72
Mason *et al*.	2003	Time to rise by 4°C	66 [§]	59 [§]
Poole *et al*.	2004	Time to rise by 4°C after immersion	71	77
Poole *et al*.	2006	Time to rise by 4°C after immersion	69.7	66.7
Infrared thermography				
von Bierbrauer *et al*.	1998	Rewarming at 30 min after immersion	58	100
Coughlin *et al*.	2001	Fingertip and finger base temperatures and their gradient at 7–9 min of rewarming	100	100
Poole *et al*.	2006	Temperature gradient between the tip and middle portion of finger after immersion	57.6	85.7

[#]Sensitivity is shown for VWF except in the study of Hack *et al*. (Vibration-induced white finger patients+ vibration-exposed subjects with tingling and/or numbness). [†]Specificity is shown for non-vibration-exposed controls except in the studies of Brubaker *et al*. (non-vibration-exposed controls+vibration-exposed controls with minimal exposure) and the studies of Pelmear *et al*. and Virokannas *et al*. (vibration-exposed controls+non-vibration-exposed controls). [§]From ROC analysis using vascular SWS stages 0V versus 1V–3V.

LDPI is an imaging modality with a distant light source and detector not allowing continuous measurement due to scanning time. In the literature, limited data are available showing the diagnostic value of laser Doppler techniques for VWF.

Under resting conditions, blood flow within an individual is subjected to physiological variation over time, and this therefore interferes with the reproducibility of microcirculation investigations[33]. This variability can be diminished if measurement of finger blood flow is incorporated with a local hot or cold provocation test. Moreover, skin perfusion is frequently characterized by large spatial variation with substantial differences in perfusion even at adjacent areas[34]. Therefore, investigation of blood flow over a small area may not represent the surrounding blood flow. The probe of the conventional LDPM in contact with the skin can record blood flow from a small skin area. This makes the representativeness of the blood flow measurement uncertain. In contrast, LDPI allows study of larger skin areas by mapping the local laser Doppler flux without direct contact and thereby eliminates the changes in microcirculation induced by pressure or movement of the LDPM probe.

LDPI produces two-dimensional color-coded images of a skin area of interest. Visualization of blood perfusion over a larger hand skin area can help in the detection of impaired digital vascular regulation in VWF patients[34]. In their study, Miyai *et al*. suggested that the LDPI is an important technique enabling quantification of finger skin blood flow response to cold water immersion and has the potential of providing detailed and accurate information to aid in the detection of peripheral circulatory impairment in the fingers of vibration-exposed workers[34].

Human hand skin microcirculation is accomplished through the superficial capillary (nutritive) network and the deeper subpapillary (thermoregulatory) network[35]. The reliable quantification of nutritive and thermoregulatory blood flow may be helpful in diagnosis of vascular

abnormality. Murray *et al*. compared red and green laser Doppler imaging of blood flow[36]. They concluded that red and green wavelengths appear to image different components of the microcirculation.

Ziegler *et al*. tested the value of laser Doppler anemometry (where the laser beam is positioned on a suitable capillary by use of a CCD camera and frequency shift of Doppler signal is detected by a photodetector) to distinguish between patients with VWF and primary RP and concluded that laser Doppler anemometry in association with an appropriate cold provocation could be useful in objective diagnosis of VWF[37].

Finger systolic blood pressure (FSBP) can also be measured by the laser Doppler technique, which can detect the return of blood flow after local digital cooling by means of a frequency shift in reflected electromagnetic waves[38]. Kurozawa *et al*. mentioned that the use of laser Doppler flowmetry can be helpful in diagnosing VWF cases with FSBP measurement after finger cooling[39]. The authors observed that laser Doppler flowmetry could demonstrate similar findings to the plethysmography. In a study using laser Doppler flowmetry, Allen *et al*. revealed a sensitivity of 81% and a specificity of 100% in diagnosing VWF[40].

Finally, for the purpose of quantifying finger skin microcirculatory flow among a vibration-exposed population, the noncontact LDPI method seems to be useful tool capable of providing data from a larger area.

Plethysmography

In the assessment of VWF patients, various techniques of finger plethysmography like arterial occlusion or venous occlusion strain gauge plethysmography and photoplethysmography have been used.

Strain gauge plethysmography (arterial occlusion)

An increase in digital arterial tone is reflected by a decrease in finger systolic blood pressure (FSBP). Patients with RP respond with a more pronounced decrease in FSBP to cooling than healthy controls. In strain gauge plethysmography, systolic blood pressure in the fingers is measured and is usually combined with local cold provocation by finger cooling. Measurement of FSBP with finger cooling is considered to be one of the most accurate laboratory modalities in objective confirmation of the diagnosis of VWF and in assessing the severity of it. The test method with FSBP measurement was introduced by Nielsen and Lassen in 1977[41]. A typical measurement includes application of suprasystolic pressure to the digit by inflating a pressure cuff (or a double-inlet cooling cuff perfused with water) connected to a plethysmograph and gradual release of the occluding cuff after a period of cooling followed by detection of blood flow indicating the maximum digital arterial (reopening) pressure[38].

Quantification of FSBP can be performed precisely; the within-day and between-day variation coefficients of FSBP are about 5 and 10% respectively[42]. For assessment of digital vascular function by measuring FSBP in subjects exposed to hand-arm vibration, the ISO has standardized the test conditions for optimal provocation, which includes reference measurement at 30°C followed by finger cooling for a period of 5 min at 15 and 10°C without or with additional body cooling[38]. Reported sensitivities and specificities of the local cooling tests with FSBP measurement by plethysmography from different studies are presented in Table 3[6, 25, 39, 43–52]. Among those reports, a good number of studies demonstrated the sensitivity and specificity of the local cooling test with FSBP measurement to be more than 80%, without additional body cooling, indicating satisfactory diagnostic performance of this method.

Quantifying cooling-induced FSBP responses of digital arteries appears to show higher sensitivity and specificity for diagnosis of VWF[53]; but in some research works, the diagnostic ability of FSBP in the assessment of vascular injury of HAVS patients has been questioned. Poole *et al*. reported a comparatively low sensitivity and high specificity: the sensitivity was between 44 and 61%, and the specificity was between 91 and 95%[51]. On the other hand, Thompson *et al*. reported a comparatively high sensitivity (94%) and low specificity (15%)[54].

Strain gauge plethysmography (venous occlusion)

Digital blood flow can be measured noninvasively by this technique. Digital venous occlusion is achieved by inflating the cuff around the finger with a pressure that is above venous but below arterial pressure. To date, there is a lack of reports indicating the usefulness of venous occlusion strain gauge plethysmography in differentiating VWF patients from controls. Future research works are needed to determine the diagnostic significance of quantifying digital blood flow by this method to assess the vascular abnormality in VWF patients.

Photplethysmography

Photocells record the changes in the intensity of backscattered light from the red cells of the skin that is transmitted from an infrared light source and determine the blood volume of the respective area[38]. Thereby, this technique permits the assessment of skin microcirculatory volume, which can be combined with a cold test by immersion of a hand/s into cold water. There are few studies with measurement of blood volume in cutaneous microcirculation for diagnosis of VWF by photoelectric plethysmography. Using a reduction of 75% in photoplethysmography as a discriminating threshold for detection of vibration-induced RP, Bogadi-Sare and Zavalic found the sensitivity to be 62% and the specificity to be 87% (Table 3)[26].

Table 3. Selected studies involving a local cold test with measurement by plethysmography for diagnosing VWF

Measurement tool & author (s)	Year of reference	Diagnostic criteria	Sensitivity (%)	Specificity[#] (%)
Strain-gauge plethysmography				
Olsen *et al*.[§]	1981	FSBP=0	92	81
Ekenvall and Lindbland	1986	%FSBP<60%	74	100
Pyykko *et al*.	1986		25	95
Bovenzi	1988	%FSBP<60%	100	87
Olsen[§]	1988	FSBP=0	74	88
Kurozawa *et al*.[§]	1991	%FSBP<90%	81.7	90.3
Virokannas and Rintamaki	1991	%FSBP<76%	50	84
Kurozawa *et al*.	1992	%FSBP<80%	88	77
Bovenzi	1993	%FSBP<60%	84	98
Bovenzi	1998	$\%FSBP_{10°C}<70\%$	100	90
		$\%FSBP_{10°C}<60\%$	85.8	93.7
Bovenzi	2002	FSBP=0	44	99
		$\%FSBP_{10°C}<60\%$	87	94
Poole *et al*.	2004	$\%FSBP_{15°C}\leq62.4\%$	43.5	95
		$\%FSBP_{10°C}\leq79.5\%$	47.6	95.2
Nasu *et al*.	2008	$\%FSBP_{10°C}\leq75\%$	73.9	82.5
Photoplethysmography				
Bogadi-Sare and Zavalic	1994	75% reduction in photo-plethysmographic amplitude	62	87

[#]Specificity is shown for vibration-exposed controls except in the studies of Virokannas & Rintamaki and Kurozawa *et al*. (vibration-exposed controls+non-vibration-exposed controls) and the studies of Poole *et al*. and Bogardi-Sare and Zavalic (non-vibration- exposed controls). [§]Studies conducted with additional body cooling.

The method of plethysmography has several limitations. The equipment is expensive and complicated, which also demands a skilled and experienced investigator to ensure the accuracy of recordings. For photoplethysmography, uncertainties still exist regarding the ability to calibrate the signal and the reproducibility of results. For strain gauge plethysmography, gauging the appearance of pulse (opening pressure) adds some degree of subjectivity to the technique[55]. Furthermore, detection of volume changes by strain gauges produces a measure that is insensitive to changes in microvasculature of the skin, the impairment of which plays an important role in the characteristic attack of VWF[56]. Despite the limitations, strain gauge plethysmography with FSBP measurements has been suggested to be valuable in the diagnosis of VWF.

The Need for Quantification of both Skin Microcirculation and FSBP in VWF

In patients with VWF, there is an impairment of skin microcirculation[57]. Gemne *et al*. suggested a defect in autonomic modulation of the feed capillary bed in VWF[58]. The abnormalities in the control mechanisms for digital cutaneous blood flow in response to cold can cause an attack of VWF. Arneklo-Noblin *et al*. posited that for many VWF cases, vascular injuries are restricted to the skin and its blood vessels rather than to digital arteries[59]. Moreover, the fact of unimproved FST among subjects with improvement in FSBP also emphasizes impaired cutaneous circulation in VWF[25,60]. Therefore, measurement of FSBP will not be able to detect the vascular abnormality in all subjects with VWF. It has been suggested that FSBP changes are secondary to changes in the total digital blood flow, whereas skin blood flow possibly reflects a rather small and variable part[61]. Therefore, for a better assessment of vascular injuries in HAVS, a test battery including measurements of both FST and FSBP is essential.

Conclusions

The data obtained with different techniques should be interpreted with caution, as the test results depend not only on the accuracy and reproducibility of the measuring equipment, but also on the test conditions and assessment parameters. Currently, for a reliable objective diagnosis of vascular abnormality in HAVS, quantification of both FST and FSBP by established methods like thermometry or thermography and strain gauge plethysmography, respectively, appears to be useful. In the evaluation of

tests with thermometry and thermography, it is necessary to establish a useful or effective parameter/s for quantification of the test results. Despite the fact that the LDPI technique seems to be a useful diagnostic tool, the existing data appear to be not enough to show its usefulness in noninvasive quantification of microvascular blood flow for patients with HAVS. In the objective diagnosis of VWF and discrimination from other types of RP, the distinctive nailfold capillaroscopy pattern needs to be evaluated further among VWF patients in future studies from different institutions. For a complete and reliable assessment of the role of a test modality in diagnosing VWF, the diagnostic performance of it could be evaluated using receiver operating characteristic (ROC) curve analysis and the area under the ROC curve (AUC). Furthermore, the diagnostic studies should report the likelihood ratios of a test that are not influenced by the disease prevalence.

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