Vascular component of hand-arm vibration syndrome: a 22-year follow-up study

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Background	Vibration-induced white finger (VWF) is often assessed using the Stockholm Workshop Scale (SWS) and cold challenge plethysmography. However, long-term longitudinal studies using both methods are scarce.
Aims	To study the long-term course and prognostic factors of VWF assessed with the SWS and photo-plethysmography (PPG), and to examine the effects of lifestyle on PPG score, regardless of VWF status.
Methods	Forty male construction workers were examined with a test battery and clinical examination in 1994 and 2016/17.
Results	At baseline, the sample comprised 27 workers with, and 13 without, symptoms of hand-arm vibration syndrome (HAVS). Thirty-five workers reported vibration exposure during follow-up. The mean age of the workers was 60 years (45–78) at follow-up. The paired *t*-test showed that PPG scores deteriorated from 1994 to 2017 in the 27 workers with HAVS in 1994 (mean difference 2.7 min, 95% confidence interval (CI) 0.2–5.2). However, there was no statistically significant change in SWS scores in these workers over time. Smoking and age were associated with PPG score deterioration. Vibration exposure during follow-up predicted SWS score deterioration: 1000 h of exposure predicted a deterioration stage of 0.09 (95% CI 0.03–0.16). Analysis of all 40 workers showed that 2017 PPG scores were associated with positive serum cotinine and self-reported smoking during follow-up.
Conclusions	Whereas age and smoking predicted a PPG deterioration, continued vibration exposure predicted worsening of white finger symptoms. The association of PPG score and smoking should be considered in diagnostic and prognostic factor evaluations.
Key words	Follow-up; hand-arm vibration syndrome; plethysmography; Stockholm Workshop Scale; white finger.

Introduction

Hand-arm vibration syndrome (HAVS) is a common occupational hazard with vascular, neurological and/or muscular symptoms [1]. The vascular component, i.e. vibration-induced white finger (VWF), is usually classified according to severity of symptoms using the Stockholm Workshop Scale (SWS) [2]. Cold provocation finger thermometry and plethysmography, such as strain gauge plethysmography and photoplethysmography (PPG), are commonly used laboratory tests for VWF. PPG [3–6] is a non-invasive optical technique that uses low-intensity light to detect blood volume changes in the microvascular tissue bed [7].

Knowledge about the long-term course and prognostic factors for VWF is important for prevention, but studies have not been conclusive. Studies have indicated that symptoms evaluated by the SWS can improve after removal or reduction of vibration exposure [8–10]. However, long-term longitudinal studies evaluating both SWS and cold challenge test scores and the influences of lifestyle factors or comorbidity are scarce [8,11,12]. Little is known about the influence of comorbidities on the course of HAVS [13]. SWS and PPG scores

are weakly correlated [3,4], and some have speculated whether they may measure two different aspects of the vascular response [3]. Whether the SWS is fit for this purpose has been discussed previously [14–16].

In this study, we aimed to evaluate the long-term course and prognostic factors of VWF using PPG and the SWS and to determine the cross-sectional effects of possible predictive factors on PPG score, regardless of previous HAVS symptoms.

Methods

In 1994, all 211 employees in two workshop units of a construction company participated in a HAVS examination [17]. The company shut down in 1999. We used responses to the 1994 questionnaire to select workers for a 2016/17 follow-up study, and these included workers who were exposed to hand-held vibrating tools at work and who had reported numbness in fingers and/or VWF attacks, or workers who were not exposed to hand-held vibrating tools and who reported no neurological or vascular symptoms. Participation was voluntary, and written informed consent was obtained. The study was approved by the Norwegian Regional Ethical Committee.

The HAVS examinations took place in Oslo, Norway, in 1994 and 2017. The 2017 study was conducted from September 2016 to March 2017. No patients were exposed to vibration for 12 h before testing. We interviewed the workers about occupational and non-occupational exposure to hand-held vibrating tools (type of tool, hours per day, days per year and number of years); smoking habits and the use of smokeless tobacco; medical conditions; medication; and neurological, vascular or muscular symptoms of HAVS. We calculated current alcohol consumption (L (pure alcohol)/year), based on self-reported consumption [18]. We staged white finger symptoms using the vascular SWS [2] as follows: Stage 0 indicated no symptoms (but including increased cold sensitivity); Stage 1 indicated white finger attacks affecting only the tips of one or more fingers; Stage 2 indicated attacks affecting the distal and middle pulp spaces of one or more fingers; Stage 3 indicated attacks affecting all three pulp spaces (distal, middle and proximal) of most fingers and Stage 4 indicated attacks that involved trophic skin changes at the finger tips.

A medical doctor (L.A.) performed PPG [7] using a PPG monitor and PicoLog software (Pico Technology, Cambridgeshire, UK). We obtained baseline PPG tracings for the third digit of the left hand at ambient room temperature between 21 and 24°C. The left hand was immersed in 15°C water for 2 min before repeating the PPG procedure, and we visually interpreted the tracings by comparing the post-immersion amplitudes to measured baseline amplitudes. We defined PPG scores as the number of minutes (range 0–25 min) until the start of improvement in the post-immersion amplitude.

We collected serum cotinine, caffeine and carbohydrate-deficient transferrin (CDT) on the day of the examination

in 2017. CDT was measured at UNILABS Laboratory (Oslo, Norway) by capillary electrophoresis using CapillarysTM (Sebia Inc., Norcross, GA, USA). The sample preparation procedure for cotinine and caffeine in the serum has been described previously [19]. However, we used two internal standards instead of one in this study. We added 100 μl of a 0.0025 mg/ml internal standard solution containing caffeine-$^{13}C_3$ and cotinine-(methyl-d_3) to 0.5 ml serum aliquots. A Dionex UltiMate 3000 Binary UHPLC system (Sunnyvale, CA, USA) and a Thermo Scientific TSQ Vantage triple stage quadrupole mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) with positive electrospray ionization were used for analyte separation and mass spectrometric detection, respectively. We quantified cotinine and caffeine by adding internal standards and by relative comparisons to spiked serum blank samples that were prepared identically. The method was evaluated over the concentration ranges of 0.75–3750 μg cotinine/L serum and 3.75–7500 μg caffeine/L serum, resulting in a correlation coefficient >0.998.

The main outcome variables were changes in the PPG and SWS scores from 1994 to 2017, calculated by subtracting baseline values from follow-up values. Scores of 0 indicated no change, positive scores indicated deterioration and negative scores indicated improvement. We defined self-reported vibration exposure as the number of hours of occupational or non-occupational exposure during follow-up and smoking as pack-years during follow-up. We measured other predictors in 2017, including age (>/<60); self-reported alcohol consumption (L (pure alcohol)/year); cardiovascular disease (self-reported cardiac disease and/or hypertension, yes/no); hypertension (yes/no) and serum cotinine, caffeine and CDT. The 2017 PPG score was an additional outcome.

We performed statistical analysis using SPSS Version 24.0 (Armonk, NY: IBM Corporation). We set the level of statistical significance at $P <0.05$. To identify the long-term course of HAVS and its predictors, we analysed the subgroup with HAVS in 1994 ($n = 27$) separately by assessing the overall change in PPG or SWS score from 1994 to 2017 (paired t-test, univariate analyses), the correlation between the change in PPG score and SWS score and the association between each predictor and a change in PPG or SWS score (linear regression, bivariate analyses). We kept statistically significant predictors in final multiple regression models, in which each of the other predictors was tested as a potential confounder and included if the predictor changed the effect estimate by >15%. The total sample size was 40. To determine the difference in clinical course between the 27 workers with HAVS and the 13 without HAVS in 1994, we estimated the association between the diagnostic group (HAVS versus no HAVS in 1994) and the change in PPG or SWS score. For the 25 non-smokers during follow-up, regardless of previous HAVS symptoms, we estimated association between vibration exposure during follow-up and change in SWS score. For the cross-sectional analyses of

the entire sample (n = 40), we determined the associations between vibration exposure during follow-up, lifestyle factors and 2017 PPG score.

We used Student's t-test or linear regression to assess associations. As changes in SWS scores were not normally distributed, we also performed non-parametric Wilcoxon signed-ranked tests and Mann–Whitney U-tests to analyse this outcome variable.

Results

Of the 110 workers who met the inclusion criteria (68 with and 42 without HAVS in 1994), two were dead and 47 could not be traced. Of the 61 invited participants, 21 declined to participate: 11 of 38 (71%) in the HAVS group, and 10 of 23 (57%) without HAVS in 1994. Reasons for declining included long travel time or lack of time. Therefore, 40 of 61 (66%) invited subjects participated in the 2017 study.

Table 1 shows the background and exposure data for the sample. Table 2 shows the vascular staging in 1994 and 2017 of the workers with HAVS in 1994 (n = 27). At baseline, four workers had only vascular symptoms, 11 had only neurological symptoms and 12 had both. Of the 16 workers reporting white finger attacks in 1994, descriptive statistics showed that seven had no vascular symptoms in 2017. Table 3 presents the exposure data grouped by a change in PPG score from 1994 to 2017.

There was <15% change in the estimates between the parametric and non-parametric tests, so we used parametric statistics. In the paired sample t-test (univariate analysis), PPG scores deteriorated from 1994 to 2017 in the 27 subjects with HAVS in 1994: mean difference 2.7 (95% confidence interval (CI) 0.2–5.2). Time to the start of improvement in post-immersion PPG amplitude after cooling (recovery) increased by 2.7 min from 1994 to 2017. The change in mean SWS score was not statistically significant. Changes in PPG and SWS scores from

1994 to 2017 were negatively correlated (Pearson's correlation = −0.51 (P < 0.01)). Therefore, only the PPG score was associated with follow-up time.

The within-assay (n = 6) and between-assay (n = 6) precisions for cotinine and caffeine were <2.9 and <9.8%, respectively. The detection limit (3σ) was 0.60 µg cotinine/L serum for cotinine and 1.7 µg caffeine/L serum for caffeine. There was one missing value for serum CDT.

We then investigated the relationship between potential prognostic factors and change in PPG or SWS score using bivariate and multivariate linear regression analyses. In the 27 workers with HAVS in 1994 (Table 4), change in PPG score was associated with serum cotinine, self-reported pack-years of smoking during follow-up (one pack-year of smoking predicted 0.5 min PPG score deterioration) and age (PPG score deterioration from 1994 to 2017 was larger in those aged >60 by 5.8 min). In the multivariate model including pack-years of smoking and age, both predictors remained statistically significant. Pack-years of smoking: unstandardized coefficient B of −0.05 (95% CI −0.09 to −0.01); age: unstandardized coefficient B of −0.068 (95% CI −0.134 to −0.003). In the linear regression analyses, the residuals were normally distributed, and no signs of unequal scatter were evident. Change in SWS score was associated with vibration exposure during follow-up, smoking and alcohol consumption (Table 4). In multivariate models including these three predictors, all remained statistically significant. Pack-years of smoking: unstandardized coefficient B of −0.05 (95% CI −0.09 to −0.01); alcohol consumption: unstandardized coefficient B of −0.07 (95% CI −0.13 to −0.003); vibration exposure: unstandardized coefficient B of 0.07 (95% CI 0.01–0.13). Also, we estimated the effect of vibration exposure during follow-up on SWS score change in the 25 non-smokers: unstandardized coefficient B of 0.053 (95% CI −0.001 to 0.107). The diagnostic group in 1994 (HAVS or no HAVS) was not associated with change in PPG or SWS score.

Table 1. Background and exposure data at participation in 2017

	Total sample (N = 40)	HAVS in 1994 (n = 27)	No HAVS in 1994 (n = 13)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	60.4 (10.3)	60.2 (10.4)	60.7 (10.5)
Hours with HAV, 1994–2017	2802 (4194)	3793 (4738)	743 (1307)
Vibration-exposed subjects, 1994–2017, n (%)	35 (88)	27 (100)	8 (62)
Cardiovascular disease, n (%)	16 (40)	11 (41)	5 (38)
Smokers during follow-up, n (%)	15 (38)	12 (44)	3 (23)
Pack-years of smoking, 1994–2017	3.8 (6.2)	4.1 (6.4)	3.0 (5.9)
Serum cotinine (µg/L) (in all)	103 (210)	103 (227)	104 (176)
Alcohol consumption (L/year)	3.4 (3.9)	3.7 (4.3)	2.8 (3.1)
Serum CDT (%) (1 missing)	0.9 (0.6)	0.9 (0.7)	0.8 (0.3)
Smokeless tobacco users, n (%)	3 (8)	2 (5)	1 (8)

HAV, hand-arm vibration.

Table 2. Vascular stage of workers with HAVS in 1994 ($n = 27$) by year of investigation

	1994	2017
SWS stage: 0/1/2/3/4 (n)[a]	11/9/6/1/0	18/4/4/1/0
SWS score (SD)	0.5 (0.5)	0.6 (0.9)
WF attacks by category (n)[b]	14/1/2/4/4/2/0	17/2/0/5/3/0/0
Photoplethysmography score (minutes) (SD)	6.9 (7.6)	9.7 (7.1)
Difficulties at work or during leisure activities due to WF (n)	8	9

Continuous variables are presented as the mean (SD), and categorical variables are presented as numbers. WF, white finger.

[a]SWS: Stage 0: no symptoms (including increased cold sensitivity); Stage 1: VWF attacks affecting only the tips of one or more fingers; Stage 2: VWF attacks affecting the distal and middle pulp spaces of one or more fingers; Stage 3: VWF attacks affecting all three pulp spaces (distal, middle and proximal) of most fingers; Stage 4: attacks that involved trophic skin changes at the finger tips.

[b]Categories for the number of VWF attacks/year: 0/1–5/6–20/21–50/51–100/100–365/>365.

Table 3. Description of workers with HAVS in 1994 ($n = 27$) according to changes in the PPG score from 1994 to 2017

	PPG score: change during follow-up	
Predictors at participation in 2017	Stable or improved ($n = 8$)	Deteriorated ($n = 19$)
	Mean (SD)	Mean (SD)
Age (years)	54.2 (10.1)	62.7 (9.7)
Hours with HAV, 1994–2017	3573 (4768)	3886 (4853)
Years since vibration stopped	7.6 (8.4)	4.9 (6.3)
Cardiovascular disease, n (%)	3 (38)	8 (58)
Pack-years of smoking, 1994–2017	0.1 (0.3)	5.9 (7.0)
Smokers during follow-up, n (%)	1 (13)	11 (58)
Serum cotinine (µg/L)	0.3 (0.0)	147 (261)
Alcohol consumption (L/year)	4.6 (5.0)	3.3 (4.0)
Serum CDT (%)	0.6 (0.2)	1.0 (0.8)

Finally, a cross-sectional analysis of the entire sample ($n = 40$) showed that the 2017 PPG score was associated with serum cotinine (µg/L), with an unstandardized coefficient B of 0.011 (95% CI 0.002–0.021) ($P < 0.05$), and with pack-years of smoking during follow-up, with an unstandardized coefficient B of 0.4 (95% CI 0.1–0.7) ($P < 0.05$).

Discussion

In subjects diagnosed with HAVS at baseline, smoking during follow-up and age were associated with deterioration in the objectively measured vascular component (PPG). Vibration exposure during follow-up was associated with deterioration in the white finger symptom score (SWS). Changes in PPG and SWS scores were negatively correlated. For those with and without HAVS at baseline, 2017 PPG scores were influenced by serum cotinine and by self-reported smoking during follow-up.

Strengths of this study include the long-term longitudinal time observation and the objective measurements, including biological samples. The use of PPG might seem obsolete [20], but use of the same PPG equipment in the longitudinal measurements is considered a major strength. Subjective evaluation of PPG amplitudes may have introduced bias. Since we have no reason to suspect differential misclassification (the researchers did not know the exposure status of participants at the time of data collection), we do not believe that such misclassification affected the results. The study included only men, which avoided confounding by sex. Of 61 invited subjects, 40 (66%) participated in the study, which is high considering the long follow-up period. Vibration exposure was based on self-reporting, which may have produced recall bias. We did not have information about vibration levels (per ms^2) of the tools, but most patients had used sanders. Regarding statistical precision, the non-positive findings may be a result of low statistical power due to the small sample size.

The SWS scale has been used for >30 years [16] and is often applied in longitudinal studies. Continued vibration exposure after diagnosis of HAVS has been associated with SWS score deterioration [8,9]. Additionally, studies have shown that VWF can improve after removal from, or a reduction in, vibration exposure [8–10,12,21,22]. In this study, the paired sample *t*-test (the performance of each subject is measured twice) showed no statistically significant change in SWS from 1994 to 2017. We

Table 4. Longitudinal analysis of workers with HAVS in 1994 (*n* = 27)

	PPG score: change during follow-up time	SWS score: change during follow-up time
	Unstandardized coefficient *B* (95% CI)	Unstandardized coefficient *B* (95% CI)
Age in 2017 (>/<60)	5.8 (1.2–10.3)*	−0.3 (−1.0 to 0.4)
HAV, in 1000 h, 1994–2017	−0.4 (−0.9 to 0.1)	0.09 (0.03–0.16)*
Number of years since vibration stopped	−0.05 (−0.52 to 0.32)	0.0 (−0.1 to 0.2)
Pack−years of smoking, 1994–2017	0.5 (0.1–0.8)*	−0.06 (−0.11 to −0.01)*
Serum cotinine (µg/L)	0.01 (0.00–0.02)*	−0.001 (−0.003 to 0.000)
Alcohol consumption (L/year)	0.05 (−0.55 to 0.65)	−0.09 (−0.17 to −0.02)*
Serum CDT (%)	1.1 (−2.5 to 4.6)	−0.2 (−0.7 to 0.3)
Serum caffeine (µg/L)	0.001 (0.000–0.002)	2.902E-5 (0.000–0.000)
Cardiovascular disease (yes/no)	−0.9 (−6.0 to 4.2)	0.5 (−0.3 to 1.1)

*$P < 0.05$. HAV, hand-arm vibration.

then investigated the effect of potential prognostic factors using linear regression analyses, in which vibration exposure during follow-up predicted deterioration in VWF. In other words, only the workers with higher vibration exposure dose experienced a deterioration in SWS score. Our results suggest that continued vibration exposure after diagnosis of HAVS predicts deterioration in SWS score, underlining the importance of reduced vibration exposure in cases of HAVS.

We evaluated several other possible predictors of change in SWS score in subjects with HAVS. No association was found with age, cardiovascular disease or time since last vibration exposure. Smoking and alcohol consumption during follow-up predicted improvement in SWS score, which could be due to cessation of smoking and drinking by workers who experienced aggravated symptoms. A Swedish study found an association between smoking and poorer SWS score [12], while other studies have not observed any effect on white finger progression [8,11,23]. No adverse effect of alcohol has been reported [8]. Our study indicated that workers with and without HAVS were not very different regarding the long-term course of white finger. Studies have suggested that improvements are more likely in milder cases of VWF [8]. Less SWS improvement has been reported in older workers [23], while another study showed less improvement in younger workers [12]. A large study by Ogasawara *et al.* showed no association between age and SWS score change [8]. Finally, an unfavourable clinical course of VWF in individuals diagnosed with cardiovascular disease was reported by Petersen *et al.* [12] but not by Ogasawara *et al.* [8].

Unlike VWF course as assessed by SWS, little is known about VWF course as assessed by PPG. In our study, change in PPG and SWS scores in workers with HAVS at baseline was negatively correlated. The diagnostic value of finger thermometry and PPG in the assessment of HAVS was discussed by Bogadi-Sare and Zavalić [24]. SWS and PPG scores were weakly correlated, and the authors suggested that they measure two different aspects of the vascular response [3].

Smoking predicted a deterioration in PPG score but not in SWS score. The mechanism underlying the effect of smoking on PPG score might be related to endothelial dysfunction and atherosclerosis [25]. Additionally, nicotine acts as a vasoconstrictor of the small blood vessels [26]. A similar association has been shown by studies measuring finger systolic blood pressure with a cuff and strain gauge technique [11,27]. Our 2017 PPG scores were influenced by cotinine on the day of testing. Although nicotine is mainly metabolized in the liver, the nicotine metabolite cotinine is regarded as the best predictor of total nicotine intake [28]. Bast-Pettersen *et al.* reported that current cotinine serum concentrations were higher in workers diagnosed with HAVS than in vibration-exposed workers without HAVS and unexposed manual workers [29].

This study found that vibration exposure had no effect on changes in PPG score. We can only speculate about the cause. Blood vessel reactivity as assessed by PPG might normalize over time in the absence of vibration exposure, while symptoms as assessed by the SWS may be related to other conditions that are not normalized in the same manner. An alternative explanation may be that workers with aggravated, subjective white finger symptoms are more likely to recall and report vibration exposure than workers without such symptoms. This recall bias may have resulted in an overestimation of the association between vibration exposure and SWS score.

Key points

- In workers with hand-arm vibration syndrome at baseline, deterioration in photoplethysmography was associated with smoking during follow-up and age.
- Deterioration in white finger symptom scores (Stockholm Workshop Scale) of workers with hand-arm vibration syndrome was associated with self-reported exposure to hand-held vibrating tools.
- On the day of the examination, photoplethysmography score in individuals with and without hand-arm vibration syndrome was influenced by serum cotinine and by self-reported smoking during follow-up.

Competing interests

None declared.

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