

Where is the research frontier for hand-arm vibration?

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GEMNE G. Where is the research frontier for hand-arm vibration? *Scand J Work Environ Health* 1994;20 special issue:90—9. A central question for current hand-arm vibration research is how to combine diagnostics with exposure evaluation so that reliable risk assessments can be made for different tools and work processes. The scientific foundation of the model, in annex A of ISO 5349, for white finger (WF) risk prediction has been shown to be insufficient. Prospective epidemiologic studies are needed to establish exposure-response relationships addressing the specific etiologic factors. Another important research field concerns WF pathogenesis, which is likely to be a vessel wall lesion causing vasodilatory deficiency. Epidemiologic research, in combination with human and animal experimentation, on endothelium-dependent mechanisms is desirable, among other things, because a therapy may be within reach. A model is presented for the manifestation of cold-triggered WF in persons with exposure to vibration and other environmental stressors as a result of lowered symptom threshold and a raised level of sympathetic activity.

KEY TERMS — autonomic nervous system, diagnostics, exposure-response relationships, local fault, pathogenesis, ISO 5349, review, sympathetic hyperactivity, vasodilatory mechanisms, white fingers.

Current research on disorders occurring among workers using hand-held vibrating tools covers the whole territory of unclarified problems, from technical and medical aspects of diagnostics to pathophysiology and exposure. The main battle, however, concerns the question of how to combine diagnostics with the evaluation of exposure in a relationship that can be used for a reliable risk assessment in work with different tools and work processes. This matter is not the least interesting because of the magnitude and complexity of its inherent problems. As far as it concerns vibration-induced white fingers (VWF), it will be the first topic of the present review. Another exciting, and relatively new, field of experimental research is described for its potential to lead to a breakthrough in the understanding of the pathogenic mechanism behind white fingers, with the bonus of possibly finding a therapeutic method.

Research on hazards related to work with hand-held vibrating tools began with the field observations in 1911 of Loriga (1), who described vascular disturbances in the hands of Italian quarry workers cutting crystalline marble with chisel hammers. The same kind of observation was later made for sandstone cutters in Indiana by Cottingham (2), who also described severe paresthesia and numbness, and Leake (3). Since then, hundreds of studies have identified the hazards connected with work with differ-

ent hand-held tools, and prevalence figures for various disturbances have been carefully mapped for a great number of occupational groups. Yet, in the area of research directly concerned with prevention, very few significant advances have been made, even after modern research methods began to be employed in the 1970s. The limits of exposure below which there is a minimal risk of being injured still cannot be stated in a way that is satisfactory for either medicolegal purposes or for practical preventive work. The situation is almost as bad concerning knowledge of how vibration executes its harmful influence on the body. This lack of insight into the pathogenic and pathophysiological mechanisms is regrettable, since it also impedes the chances of finding a therapy.

More comprehensive surveys of current knowledge on these questions, as well as the occurrence, pathogenesis, and pathophysiology of vibration-induced disorders in general, have been given in other recent reviews (4—5).

Quantitative relationship between white fingers and vibration exposure

Criteria research

For decades, the search for data on which to build criteria has been given priority — rightly so, because decisions with far-reaching consequences for guidelines for prevention depend on what is practically attainable and economically justifiable within some sociopolitical framework. National recommendations on exposure limitations, ideally, should be scientifically valid and accurate, since labor inspectorates cannot enforce the law efficiently in the absence of reliable documentation.

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Value of cross-sectional studies

For the last 50 years, hundreds of studies have asked the same question: How many persons with white fingers are there in a certain occupational group? Such cross-sectional studies on prevalence are mostly of domestic interest only — for the companies employing the workers and for the authorities concerned with occupational safety and health in the countries where the studies are made. But the accumulated data from a great number of these investigations have given a useful overview of the problem, one that allows the beginning of a formulation of a theory about the quantitative relationship between exposure and disorder. Cross-sectional studies do not yield data of use for the construction of occupational exposure limits, but they reveal, for instance, that the occurrence of white fingers varies with type of tool and type of work process.

Another clear inference that can be made from cross-sectional investigations is that the prevalence varies greatly, not only between but also within occupational groups. This is a result of the great variation in susceptibility to harmful influence from various environmental stressors and biodynamic factors. If authorities do not take this fact into consideration, their regulations will become pseudoscientifically accurate.

Cross-sectional studies can sometimes give valuable information concerning specific hazards. An example is a sudden increase in white-finger prevalence when the material of the wheel used by pedestal grinders in Finland was changed to zirconium-corundum instead of corundum only (6). A technical analysis of the new wheel led to the conclusion that the increased prevalence was partly caused by impulse vibration. Another instance is the suspicion coming from a study of riveters in an airplane factory (7–8) that high-frequency vibration above the limits of the present measurement standard, the ISO 5349 (9), may be of importance for the occurrence of white fingers. Yet a third indication of a new mechanism, with interesting implications for prevention, is the greater hearing loss of persons with VWF than of vibration-exposed but symptom-free persons (10, 11).

International standard

What has been done to establish vibration exposure levels useful for quantitative recommendations? The International Organization for Standardization (ISO) began its work on the development of a standard for the measurement and reporting of hand-arm vibration already in the middle of the 1960s. After many drafts and revisions, the current standard was published, in 1986, under the name *Mechanical Vibration — Guidelines for the Measurement and the Assessment of Human Exposure to Hand-Transmitted Vibration* (ISO 5349) (9).

Concept of frequency weighting

The main feature of ISO 5349 is its frequency weighting. It implies that, as the vibration frequency rises above 16 Hz, the harmful effects of hand-arm vibration on the human organism are thought to decrease steadily by 6 dB per octave. The tacit pre-tension is that this postulate applies to all kinds of vibration injury. When the basis for it is scrutinized, however, it turns out to have a direct connection only with neurological functions. It goes back to experiments on vibration perception — the subjective reaction to vibration exposure of the hand (12) — where the subjects pressed one hand against a vibrating surface and described the sensation elicited by vibration of various frequencies between 3 and 300 Hz. The variables studied were the intensity needed to give rise to an unacceptable decrease in comfort ("tolerance limit") and the intensity at which the limit of "unpleasantness" during a 10-min exposure was surpassed. On the basis of the observations, an "equal sensation contour" was approximated that expresses the frequency dependence of the sensation perceived. In the ISO work, this — together with data from similar studies — eventually resulted in frequency weighting.

Relevance of frequency weighting for white-finger risk assessment

Measurements according to ISO 5349 are chiefly made to monitor tool vibration in a reproducible and reliable way. The implicit question underlying all measurements, however, is whether the measured value is too high to be safe. In epidemiologic studies assessing white-finger risks, such questions are explicitly posed on the basis of vibration measurements according to ISO 5349. However, in the case of white fingers, to use such values for this purpose may in fact be irrelevant a priori, since the frequency-weighting curve of the standard only relates to *acute sensory effects* rather than to *chronic peripheral vascular functions*. In addition, the experiments described recorded only the acute reaction to vibration, and there is no epidemiologic documentation of a relationship between this and the development of chronic injuries, either vascular or neurological.

Exposure-response diagram in annex A of ISO 5349

Use of ISO 5349 measurements in risk assessment models. The use of ISO 5349 for measurements in risk assessment may be doubly irrelevant. ISO 5349 has annex A, which, it should be emphasized, is not a part of the standard. It contains a diagram describing an idealized statistical relationship between white-finger latency in occupational groups, whose members have been working with one type of tool or in one industrial process, and the mean acceleration level of the tool typically used in the group. This so-called exposure-response relationship — here

termed ER 5349 — is based on seven pairs of latency and acceleration values, shown as dots in figure 1. They have been selected from among data published in 15 reports of white-finger prevalence studies in various occupational groups carried out during the period 1946–1978 (here called “the basic studies”). The 50th percentile represents the line of regression of these values, the other percentiles being constructed with the help of their standard deviation (13–15). Thus, for instance, according to this model, an acceleration of $2.9 \text{ m} \cdot \text{s}^{-2}$ would correspond to a white-finger prevalence of 10% after 10 years of exposure (dotted line).

This diagram has been extensively used to reach conclusions concerning the risk for harmfulness of vibration from certain tools with respect to white fingers. One common way is illustrated with data from a study of white fingers among Italian stone-cutters (16). The 4-h equivalent acceleration of the tool used by a subgroup of that population, who had been working only with pneumatic drills, was $23 \text{ m} \cdot \text{s}^{-2}$, corresponding to a latency of 1.7 years, as read from the 25th percentile line in ER 5349. The latency actually observed, however, was as long as 17 years for 25% of the work force. As a possible reason for this large disagreement, the author suggested *either* that the frequency-weighting curve of ISO 5349 is not representative of the risk connected with vibration from percussive tools *or* that ER 5349 is inadequate for short exposures or for intermittent work with numerous short breaks that is common for these tools.

Agreement of model “predictions” with observed prevalences. In most of the many occupational groups studied for the purpose of evaluating the precision of ER 5349, there has been a considerable discrepancy between what could be “predicted” (in terms of prevalences or latencies) and what was actually observed. In light of what will be mentioned in the following few paragraphs, this discrepancy is not surprising, since ER 5349 does not stand up well to scientific scrutinization and in some respects seems to be the result of premises and postulates made, as it were, between the thumb and the index finger. Thus, for some tools and for some work processes, ER 5349 is not likely to offer sufficient protection against white fingers, but it is also highly probable that some workplace changes previously made on the basis of ER 5349 considerations may have been redundant or have not had the desired effect.

Shortcomings of ER 5349. A revision of ER 5349 is therefore badly needed, and such a revision requires much additional research. The reader may appreciate the necessity of this — and, at the same time, get an indication of what direction new research should take — from the following description of the essential points for which the scientific documentation of ER 5349 is inadequate or lacking. A detailed evaluation has been published elsewhere (5). The term “model descriptions” used in the following text refers to the publications in which the

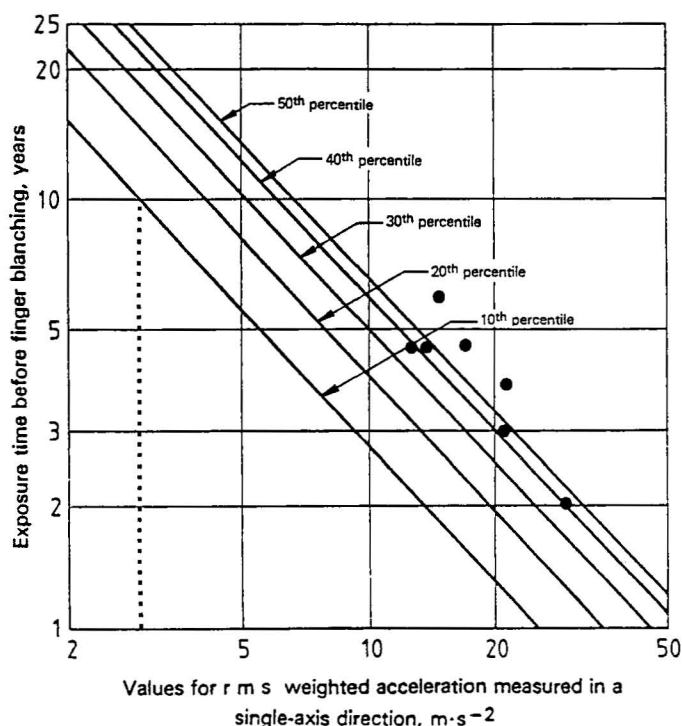


Figure 1. Model for the relationship between hand-arm vibration exposure and the latency of white fingers in occupational groups that have worked with one type of tool or in one industrial process (11, 13–15). The dots represent pairs of latency and acceleration values selected from a number of reports, on the basis of which the model was constructed (13). (rms = root-mean-square)

author has explained the construction of the model (13—15).

Choice of study variable. Latency – The choice of latency as a response variable can involve “recall bias,” (ie, a systematic error due to the inability of recalling accurately the time of onset of symptoms indicating white fingers). The possibility of this kind of bias is particularly likely to exist for a slowly developing condition like white fingers. In one of the basic studies it was stated that only 67% of the subjects could give information on symptom onset.

Latency (particularly mean latency) must also be regarded already *a priori* as less suitable for exposure-response relationships to be used in preventive work because latency data exist only for those individuals in an occupational group who have developed white fingers and it is hardly appropriate to use such values for recommendations concerning exposure limitations, which obviously should be based on the risk picture of the total group. Some group members are not affected at all, and the occurrence of white fingers after a still longer time and stronger exposure than that of the occupational groups concerned in the basic reports is unknown. Because they only represent persons with white fingers, the latencies predicted by ER 5349 overestimate the true group risk. The magnitude of this overestimation cannot be decided. (It would have been more appropriate to use the median value of the latency as the response variable, but then it would not have been possible to use the variance for the construction of the lines of prevalences in the diagram.)

Healthy worker effect – Although the latency model leads to risk overestimation, an opposing effect may also have been present in the occupational groups investigated, namely, the healthy worker effect. In general, this possibility has not been properly taken into account in the basic studies. There is, of course, no way of knowing to what extent either of these two opposing tendencies will counteract the other in a particular occupational group to which the prediction model is applied.

Effect modifiers, confounding factors, and diagnostics. Individual susceptibility – Factors related to the vibration-exposed person (especially individual susceptibility) may modify the effect of vibration, and confounding factors (such as variations in work methods and other ergonomic factors in the work environment) may make it difficult to interpret correctly the prevalence figures observed in a particular occupational group. The author of the model referred to the distribution of the reported latencies as approximately normal, which was taken to ensure that the influence of effect modifiers and confound-

ers had been taken into proper account in the model construction. There is, however, no way of knowing, for instance, to what extent individual susceptibility to harmful influence from vibration is normally distributed.

Diagnosis – The diagnostic criteria for white fingers have varied over the years. Circulatory disturbances other than those induced by vibration may have been included in some of the basic studies, namely, primary Raynaud's phenomenon and a general tendency towards low peripheral blood flow in the extremities.

Evaluation of exposure. Vibration measurements – Some of the basic studies lack data on vibration measurements on the tools used during the latency periods reported. In some cases, it may have been possible to make an estimation of acceleration levels — with considerable uncertainty because of insufficient data (although perhaps of the correct magnitude). In other studies, no acceleration data had been given. In the latter cases, it seems that the exposure estimates used for ER 5349 have been based on extrapolations from other (nonspecified) data or, perhaps, on analogy deductions with the help of assumed exposure similarities between occupational groups. However, if this is the case, it has not been stated in the model descriptions.

Measurement methods – There is a general uncertainty, the magnitude of which cannot be estimated, concerning the validity of the exposure data given in some of the basic reports because the measuring equipment or methods used at the time may have caused systematic or random measurement errors. Variations in, for instance, work methods, the condition of grinding wheels, effective daily exposure, and the employment durations of different individuals have been only briefly commented on in the discussion of the validity of the exposure-response relationships. The difficulties involved in making accurate measurements in some of the basic studies were described by Hempstock & O'Connor (17—18).

Severity of symptoms – Brammer introduced a variable, “latency ratio,” which is independent of exposure and which would therefore allow the utilization of studies that lacked reliable exposure data. This ratio was defined as the quotient between (i) the arithmetic mean latency of persons in stage 3 and (ii) the arithmetic mean latency (which, by definition, means stage 1) of the study group. The usefulness of this variable was accepted because it was considered to be approximately normally distributed and

therefore could be specified by its mean and standard deviation. Its reliability, however, is unclear because of the lack of information in the basic studies on latencies in stage 3. Such data seem to be reported only in one study in a way that allows a definite correlation of the value with the mean vibration acceleration level of the persons in question. Although the latencies of stage 3 were reported for some occupational groups, acceleration data for the corresponding individuals cannot be identified as coordinates for any of the seven points in figure 1.

"Homogeneous exposure" – ER 5349 requires the investigations included to have studied white-finger occurrence in "homogeneous" occupational groups. This requirement was regarded as having been satisfied if the groups had used only one type of tool, for instance, a chain saw, grinder or rock drill, or if they had worked in one type of industrial process. In several other respects (in relation to ergonomics and work processes) there may, however, have been important differences between the groups, resulting in incomparability between the groups from the viewpoint of risk for injury.

Exposure dose – Valid exposure-response relationships require knowledge of the intensity of the exposure over time. The ideal is a dose measure based on a combination of effective exposure time (in hours per day, days per year, and number of employment years), and the acceleration level corresponding to the particular tool type and work process. The uncertainty concerning the dose magnitude inherent in investigations of vibration injury is often due to a lack of information on relevant exposure conditions and other essential work environment factors.

In the construction of ER 5349, the only reference to exposure duration is the requirement that the occupational groups have worked with their tools "almost daily" and during the whole day. It is, however, not stated whether effective exposure is referred to (ie, the time during which the vibrating tool has actually been in close enough contact with the hands of the operator for the vibration to be transmitted to any significant degree).

Exposure duration and intermittency – One of the requirements for the inclusion of a study in the model construction was that the mean exposure time exceeded the mean latency of the group, but a minimum latency length was not required. The influence of this omission on the model is unclear. It is probable, however, that, in cases with very short latencies, also factors other than vibration — ergonomic, biodynamic and biomechanical factors as well as physical and psychological stressors — may have played a contributory role in the etiology.

The extent of intermittent exposure, with shorter or longer breaks during which the organism is allowed time for recovery, is also a parameter that needs to be quantified in estimates of exposure dose. In the model descriptions, no information is given on how this issue was taken into account.

Low exposures – Despite the fact that the model was based on studies in which none of the accelerations have been less than about $12 \text{ m} \cdot \text{s}^{-2}$, all of the percentile lines in the standard eventually published are extrapolated so that they concern accelerations of less than about $3 \text{ m} \cdot \text{s}^{-2}$. Somewhere in this low range, however, the percentile lines must in fact begin to deviate upwards, since nobody acquires white fingers from zero exposure. The uncertainty concerning the efficiency and justification of exposure limitation measures therefore gradually increases (at an unknown rate) with lower acceleration levels around, say, $5 \text{ m} \cdot \text{s}^{-2}$, which are not uncommon in many occupational groups.

Implications for further research

The matters discussed for which the model construction lacks in accuracy or relevance illustrate well what must be taken into account in research aiming at establishing reliable exposure-response relationships.

Longitudinal studies. One major lesson is that the desired data cannot be sought in cross-sectional investigations; another is that research is needed to establish exposure-response relationships for the specific risk factors associated with *various types of tools, work processes, and work methods*, as well as with biodynamic and biomedical factors. The only really rewarding method of obtaining reliable and decisive information on what factors are hazardous — and how they relate to exposure quantitatively — is to make prospective studies. In these studies, the occurrence and magnitude of various environmental factors can be monitored continuously, and medical examinations can be carried out over a period sufficiently long for significant conclusions to be reached.

Exposure dose evaluation. Technically, a correct evaluation of the exposure dose is one of the imperatives, and this evaluation is possible only in prospective studies, in which not only the acceleration, but also the duration of contact between the tool and the hand can be registered correctly. The collection of data should be made without frequency weighting in a way that permits later vibration analysis also outside the frequency range of ISO 5349. For certain tool types, the content of shocks (impulse vibration) must be especially monitored and analyzed. The ongoing revision of ISO 5349 will contain special

recommendations for the collection of data to be used in epidemiologic exposure-response studies.

Choice of diagnostic parameter. A medical parameter must be chosen carefully so as to optimize the correct identification of the disorder or symptom studied. This statement means that the diagnostic method must have good sensitivity, specificity, and reproducibility. In the case of white fingers, this requirement, in fact, is not well satisfied in a clinical examination alone. At present, one laboratory test may make the clinical (anamnesic) diagnosis a little more reliable, namely, finger systolic blood pressure measurements according to what is called the critical opening pressure method.

Confounding factors and effect modifiers. All relevant environmental agents must be considered, and proper attention must be paid to confounding factors and effect modifiers, some of which are related to the individual. In addition, the possible influence of stressors other than vibration should also be borne in mind.

Complementary follow-up studies. Results from another type of longitudinal investigation may to some extent complement the very resource-demanding and time-consuming studies that have been described. This is the follow-up study, in which defined groups of workers are examined with respect to the occurrence of disorders, on an initial occasion and then again after a period of some years. It requires, however, continuous monitoring during the follow-up period of the exposure in the same way as in a true prospective study, and it often cannot take into account exposures to various environmental factors and conditions prevailing prior to the initial examination. One follow-up study is under way in Sweden, based on a cohort of platers (19–20), with white-collar workers without vibration exposure in the same company as referents. All of the subjects are being medically examined with respect to vascular and neurological disturbances, and, in parallel, exposure is being monitored through vibration measurements and time-keeping studies.

Fate of the current standard

What will be the fate of the current standard and ER 5349? An international standard is not changed overnight, so both the standard and ER 5349 are here to stay for many years. Work on a revision of the standard has, however, started in which several of the matters presented in the preceding discussion should be considered. In the words of the report from a recent meeting of the working group for hand-arm vibration (21), it was “generally agreed that the annex implied greater precision than justified by the epi-

demiology . . . because of the non precise evaluation of the all the factors involved.” The revision should also incorporate into the lines of the ER 5349 diagram a certain “fuzziness,” which would better reflect the uncertainties inherent in the curves.

While the data from longitudinal studies that allow the establishment of new exposure-response relationships for various tools and work processes is being waited for, vibration exposure should be reduced as much as possible wherever possible. In parallel with this endeavor (for which a standard is not really needed), ER 5349, for all its scientific inadequacy, should continue to serve as a moral beacon stimulating manufacturers to produce tools that vibrate less and urging employers to alter work so that the total duration of effective exposure is reduced. There is a number of practical ways to accomplish these goals (5) and, in that process, to give priority to minimizing exposure to impulse vibration, as well as increasing the awareness of the danger possibly connected also with frequencies higher than the upper limit of the present ISO 5349.

Pathogenesis and pathophysiology of white fingers

Another urgent issue for vibration researchers, and a particularly intriguing one, is the question of the nature of the primary lesion in VWF: is it due to sympathetic hyperactivity, is a damage to the finger skin vessel wall (a “local fault”) responsible for the finger blanching, or are perhaps both these things required?

Sympathetic hyperactivity

There is reason to believe that, in fact, an imbalance between the parasympathetic and sympathetic parts of the autonomic nervous system — typically expressed as an elevation of the level of sympathetic activity — exists as a chronic trait in some persons who have been exposed for a long time to strong hand-arm vibration (22–24). Observations of more pronounced hearing loss in persons with VWF than in vibration-exposed but symptom-free subjects (9–10, 25–28) point in the same direction, that of “autonomic dysfunction.” Japanese studies (29, 30) have shown a greater occurrence of coldness and reduced skin temperatures in the toes of vibration-exposed groups, as compared with those without exposure, and these symptoms occur in the absence of acute exposure to cold or vibration. This finding also indicates a chronic general elevation of sympathetic activity. The medial muscular hypertrophy observed also in small skin arteries of the toe in patients with VWF (31) may be an effect of long-term exaggerated vasoconstriction due to sympathetic hyperactivity.

This view is part of the Japanese notion of vibration disease as an expression of autonomic dysfunction.

tion because of injury to the limbic system (especially the hypothalamus) and the cerebral cortex. The injury is thought to be the result of adaptation to repeated and long-term exposure to various environmental vasoconstrictory stressors (32, 33). Both theories are in accordance with previous suggestions concerning the multifactorial etiology of VWF (34) that such exposure may raise the level of sympathetic activity so that the symptom threshold with respect to Raynaud's phenomenon is surpassed even with fairly normal cold stimulation.

Local fault

What has been said in this presentation does not rule out a local fault as decisive for producing VWF, nor does it necessarily mean that abnormally strong sympathetic efferents to the skin vessels is enough to produce white fingers. In fact, the present picture, emerging from research over the last two decades, sees sympathetic hyperactivity as only one of several possible mechanisms leading to this disorder. Thus, in addition to being predominantly triggered by "hyperreactivity" of the central sympathetic nervous system, VWF, according to Olsen (35), may have other pathophysiological explanations as well: "active" processes, mediated by local, humoral or central sympathetic reflex mechanisms, and "passive" processes, for instance, thromboembolism in a vessel with damaged endothelium, or changes in the viscoelastic properties of the arterial wall and its response to cold. Additional possible pathogenic mechanisms were suggested, such as abnormal adrenergic receptor activity of the smooth muscle cell or hypertrophy of vascular smooth muscle cells that may contribute to some extent.

As will be treated in more detail later, these statements summarize the multifactorial view now most commonly favored. The notion of a lesion in the vessel wall is also presented, for which some recent studies have found support. These research results will be described in the following.

Damage to the vasoregulatory functions of vessel walls. Observations of the importance for normal vasodilatation of an intact endothelium (36) have had consequences also for research on possible vibration damage. Attention, quite naturally, became focused on anatomical structures and functions in the endothelium of the vessel wall as plausible targets for harmful effects of hand-arm vibration. The damaging mechanism may be of a mechanical nature, but other factors in the work environment, such as cold, may contribute.

Adrenergic vasoregulatory mechanisms. A set of adrenergic vasoregulatory mechanisms operates in the finger skin. Important observations on these functions have been made in studies by Ekenvall and her

collaborators, in which vasoactive substances were administered to the finger skin by iontophoresis (37). The findings suggested that Raynaud's phenomenon in persons damaged by vibration is caused by a selective damage to alpha-1 receptors, resulting in abnormally strong vasoconstrictory response to skin cooling from a predominance of alpha-2 adrenoceptors. In other similar experiments (38, 39), it was concluded that vasoconstriction on local cooling in the human finger skin is mainly mediated by alpha-2 adrenoceptors and that substances inhibiting them may be of therapeutic value in patients with VWF. No suggestion was given as to how this selective damage to one type of receptor but not to another residing in the same vasculature would have taken place.

Endothelial damage. An interesting indication that an actual anatomical or functional lesion is located in the wall of the finger skin vessel comes from the results of recent experiments (40) with iontophoresis of sodium nitroprusside and methacholine into the finger skin of chain-sawyers who had never experienced white fingers, those who had had white fingers up until two years earlier, and subjects with current white fingers. The blood flow was assessed with the laser-Doppler technique.

The background of these experiments is that, in the endothelial cell of the skin vessels (figure 2), two vasodilatory mechanisms operate on the basis of the endothelial-derived relaxing factor (EDRF) and prostacyclin (prostaglandin I₂). Acetylcholine — as well as the methacholine of the experiment — stimulates the release of EDRF, which reduces the calcium available for smooth muscle contraction by increasing the activity of guanylate cyclase and cyclic guanosine monophosphate. The same vasodilatory effect is mediated by nitric oxide — and the nitroprusside that releases nitric oxide — along two paths, both aimed at adenylate cyclase and cyclic adenosine monophosphate, one directly on the muscle cell and one by stimulating prostacyclin.

In their capacity as vasodilators, both methacholine and sodium nitroprusside elicited an increase in blood flow in the majority of subjects.

The most interesting finding was that the vasodilation in response to methacholine — but not to nitroprusside — was considerably weaker in the combined group of persons with current or previous white fingers than in the symptom-free group. This finding agrees with the physiological premises already described. It would also be consistent with the notion of endothelial damage that causes a deficiency in vasodilation due to a disturbance of the EDRF-mediated vasodilatory function. As indicated in figure 1, methacholine induces relaxation only through EDRF, while nitric oxide also has direct access to the smooth muscle.

The relative increase in blood flow during methacholine iontophoresis was greater in the symptom-

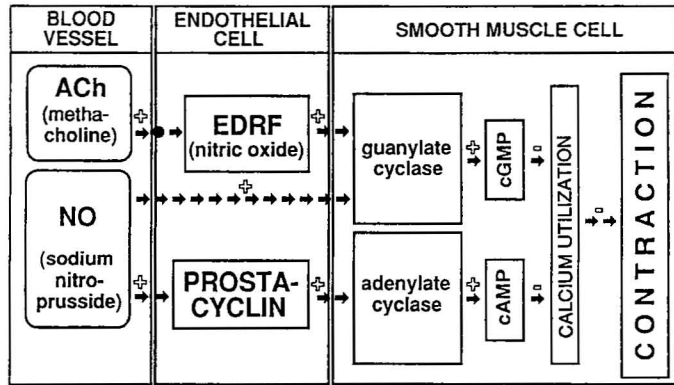


Figure 2. Endothelial vasodilatory mechanisms (44).

free group than in the group of subjects with previous white fingers, and the response in the latter group was greater than that in the symptom-free group. This gradient suggests that other vasodilatory mechanisms may have compensated for the loss of vasodilation suffered by a deficiency in endothelial smooth-muscle relaxation. This notion of a gradual functional restitution by compensatory mechanisms is also consistent with yet another observation, namely, that the vasodilatory response to sodium nitroprusside was smaller in the combined group of symptom-free subjects and persons with previous white fingers than in the group with current white fingers.

In light of recent advances in the knowledge of possible pathogenic mechanisms, the described

model (34) may be complemented to explain not only Raynaud's phenomenon, but also abnormally strong vasoconstriction in persons who have used hand-held vibrating tools for a long time (figure 3).

Figure 3 describes how, in a normal individual without habitual exposure to environmental (and generally vasoconstrictive) stressors, acute cold stimulation causes a transient rise of the sympathetic efferens to the skin vessels, but the symptom threshold (with respect to Raynaud's phenomenon) is not surpassed (A). In workers using hand-held vibrating tools an *elevation of the general level of sympathetic activity* may take place due to influence from physical and psychological stressors which cause repeated acute rises in sympathetic efferens. The relative role

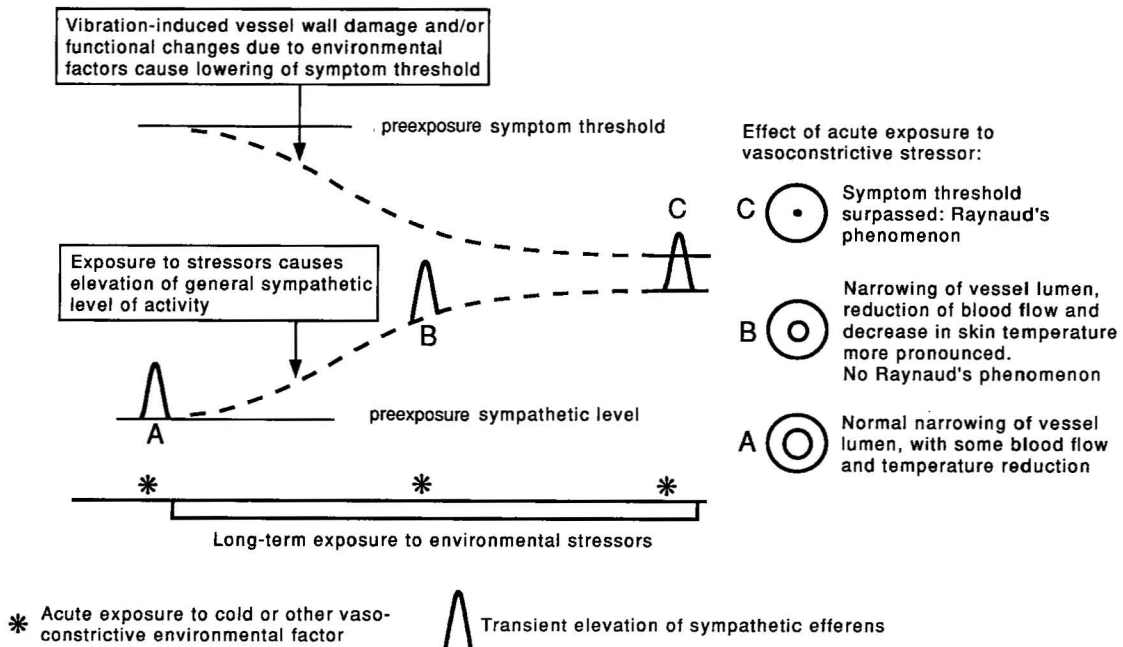


Figure 3. Model for the occurrence of abnormally strong vasoconstriction and Raynaud's phenomenon in workers using hand-held vibrating tools.

of vibration and other stressors has not been quantified.

During this prolonged exposure to environmental stressors, *the symptom threshold is lowered*. This occurrence may be due to either or both of the following processes: (i) mechanical vibration-induced damage causing endothelial injury or changes in receptor functions; (ii) changes in blood flow caused by other environmental factors or by processes secondary to endothelial damage (eg, platelet aggregation and increased viscosity).

In this period, a similar cold stimulation (B) leads to more pronounced vasoconstriction (interpreted as a sign of "cold hypersensitivity").

A combination of the two trends (sympathetic elevation and threshold lowering) eventually causes the normal cold-induced rise in sympathetic efferens (C), now starting from a higher platform, to surpass the lowered symptom threshold, and Raynaud's phenomenon occurs.

The potential effect of elevated sympathetic activity level is the same as that of a lowering of the symptom threshold. As soon as the gap between the two curves becomes sufficiently narrow, Raynaud's phenomenon may appear in response to cold stimulation. The model does not distinguish between these alternatives, which may also operate in combination. Both have been demonstrated, but neither has been ruled out.

Further research needs

The recent findings described in this presentation have increased the understanding of what goes on in the endothelium and smooth muscle cells of a vessel that adapts to environmental cold. To pursue further this kind of research is desirable, not the least because a therapy may be within reach. Rapid results may not be expected, though. Physiological experiments on peripheral circulation are very difficult because of the complexity of vascular response to cold (41). Most of the known vasoregulatory systems (adrenergic, cholinergic, purinergic, and serotonergic) have been shown to interact with each other and with endothelium-dependent substances such as nitric oxide and EDRF. Prostacyclin, as well as endothelin, a potent vasoconstrictor, relates to many of these systems. It is therefore not easy to imagine what would be the ideal design for experiments that could give a final answer to our questions, and no single theory is likely to offer the sole explanation for VWF pathophysiology. However, a combination of experimentation on humans and animals — helped by epidemiologic studies identifying high-risk individuals, tools, and work processes — may prove fruitful.

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