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LOGO HÄR

MYOCARDIAL INFARCTION
AND CARDIAC REGULATION IN
RELATION TO VIBRATION EXPOSURE

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Säll är den som har till rättesnöre
att man bör nog tänka efter före.

Tage Danielsson 1928-1985

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ABSTRACT

Myocardial infarction is the most common cause of death among middle-aged men and women in Sweden. The major established risk factors for acute myocardial infarction are related to lifestyle, e.g. smoking, obesity and hypertension. During the past few decades, the relation between various environmental exposures and myocardial infarction has also been addressed. The physical stressor, vibration, has been mentioned as one such possible occupational risk factor. One theory for pathomechanism is that exposure to vibration might cause a temporary and/or permanent disturbance in autonomic balance, thereby affecting cardiac regulation.

The purpose of this thesis was to assess the possible risk of myocardial infarction in work entailing exposure to vibration, and to study whether there is any relation between short-term exposure to vibration and cardiac regulation.

Epidemiological methods were applied to investigate a possible association between occupational exposure to vibration and myocardial infarction. Two study populations were used; one case-control study (n=475) and one cohort of iron-ore miners in Kiruna and Malmberget, Sweden (n=13621). In the former, the cases were first-time myocardial infarction patients and the controls were selected to match for sex, age and hospital catchment area. Job-exposure matrixes for vibration were established for both the case-control study and the cohort study.

In order to study acute effects on cardiac regulation, an experimental study was conducted on healthy subjects (n=20) who were exposed to hand-arm vibration exclusively and in combination with exposure to noise. The effect on the autonomic balance and thus cardiac regulation was measured by heart rate-variability.

In the case-control study, an increased risk of contracting myocardial infarction was found among occupations entailing vibration exposure. The results from the iron-ore mine cohort show an increased risk of myocardial infarction mortality compared to a reference population. The increment was higher for those younger than 60 years. Relative risks for myocardial infarction mortality increased with increasing exposure to vibration in the group at working-age and the increased risk remained after adjusting for exposure to dust. In the experimental study, exposure to hand-arm vibration was found to acutely affect the autonomic nervous system as the total heart-rate variability decreased during exposure to hand-arm vibration.

To conclude: work entailing exposure to vibration is a risk factor for myocardial infarction, increased myocardial infarction mortality attributed to exposure to vibration seems to be mainly observed at working-age, and exposure to hand-arm vibration acutely decreases heart-rate variability and thus affects heart-rate regulation.

SVENSK SAMMANFATTNING (SUMMARY IN SWEDISH)

Hjärtinfarkt är idag den vanligaste dödsorsaken bland medelålders män och kvinnor i Sverige. De riskfaktorer för hjärtinfarkt som främst nämns är kopplade till livsstil såsom rökning, fetma och högt blodtryck. De senaste årtiondena har även riskfaktorer kopplade till olika exponeringar i både den yttre miljön och arbetsmiljö omnämnts, däribland exponering för vibrationer. Tänkbara sjukdomsmekanismer är ännu oklara, men en hypotes bygger på att vibrationsexponering orsakar akut och/eller permanent påverkan på autonoma nerver och därigenom stör den autonomt styrda hjärtregleringen.

Syftet med avhandlingen var att undersöka om arbete med vibrerande maskiner ökar risken för hjärtinfarkt, samt att studera om korttidsexponering för vibrationer akut påverkar hjärtregleringen.

För att studera tänkbart samband mellan arbete som innebär exponering för vibrationer och risker för hjärtinfarkt användes två olika studiegrupper. I en fall-kontroll studie jämfördes 218 individer som fått hjärtinfarkt med 257 kontroller matchade för ålder, kön och bostadsort. Den andra studiepopulationen bestod av knappt 14000 män anställda inom järnmalmgruvorna i Kiruna och Malmberget. För båda studiegrupperna gjordes matriser för beräkningar av vibrationsexponering. För att studera akut effekt på hjärtreglering utfördes en experimentell studie. 20 friska försökspersoner exponerades för hand-arm vibrationer och effekten på det autonoma nervsystemet studerades med hjärtfrekvensvariabilitet.

Resultaten visade på en ökad risk för hjärtinfarkt bland individer som arbetar med vibrerande maskiner och/eller verktyg. Bland anställda inom gruvorna fanns i en ökad risk för död i hjärtinfarkt jämfört med en referenspopulation, en ökning som var större för de i arbetsför ålder (yngre än 60 år). Vidare framkom att risken för hjärtinfarkt kopplat till arbete som innefattar vibrationer kvarstod även efter justering för dammexponering. Resultaten i den experimentella studien visade att exponering för hand-arm vibrationer gav en akut minskning av hjärtfrekvensvariabiliteten.

Sammanfattningsvis visar resultaten att arbeten som innefattar vibrationsexponering ökar risken för hjärtinfarkt, den ökade risken verkar vara kopplad till yrkesverksam ålder och att exponering för hand-arm vibrationer ger en tillfällig minskad hjärtfrekvensvariabilitet och därmed också påverkan på hjärtreglering.

ABBREVIATIONS

AM	Arithmetic mean
ANS	Autonomic nervous system
CI	Confidence interval
CVD	Cardiovascular disease
ECG	Electrocardiogram
GM	Geometric mean
HAV	Hand-arm vibration
HPA	Hypothalamic pituitary adrenocortical
HR	Heart rate
HRV	Heart-rate variability
IHD	Ischemic heart disease
JEM	Job exposure matrix
MI	Myocardial infarction
OR	Odds ratio
PM _{2.5}	Particulate matter that passes through a size-selective inlet with a 50% efficiency cut-off at 2.5 microns aerodynamic diameter
PM ₁₀	Particulate matter that passes through a size-selective inlet with a 50% efficiency cut-off at 10 microns aerodynamic diameter
P _{TOT}	Total power density (entire frequency spectrum)
P _{HF}	Total power density in the high frequency area
P _{LF}	Total power density in the low frequency area
P _{VLF}	Total power density in the very low frequency area
RR	Relative risk
SA-node	Sinoatrial node
SAM	Sympathetic adrenal medullary
SMR	Standardised mortality ratio
VWF	Vibration-induced white fingers
WBV	Whole-body vibration

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I** Björ B, Burström L, Nilsson T and Reuterwall C. Vibration exposure and myocardial infarction incidence: the VHEEP case-control study. *Occup Med* 2006;**56**:338-344.
- II** Björ B, Burström L, Karlsson M, Nilsson T, Näslund U, and Wiklund U. Acute effects on heart rate variability when exposed to hand transmitted vibration and noise. *Int Arch Occup Environ Health* 2007;**81**(2):193-9.
- III** Björ B, Burström L, Jonsson H, Nathanaelsson L, Damber L, and Nilsson T. Fifty-year follow-up of mortality among a cohort of iron-ore miners in Sweden, with specific reference to myocardial infarction mortality. Accepted for publication online first in *Occup Env Med*.
- IV** Björ B, Burström L, Eriksson K, Jonsson H, Nathanaelsson L, N and Nilsson T. Myocardial infarction mortality in relation to exposure to vibration and dust among a cohort of iron-ore miners in Sweden. Manuscript

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BACKGROUND

Exposure to hand-transmitted vibration can cause acute effects on nerves (1), muscles (1), heart-rate regulation (2) and changes in peripheral vascular flow (3). Occupational exposure to hand-held vibrating tools is associated with permanent damage to nerves (4), vascular function (vibration-induced white fingers, VWF) (5, 6), and muscles and bones in the upper limbs (7, 8). Disorders related to whole-body vibration exposure are mainly pain in the lower back and shoulder region (9).

Construction, mining, and the forestry industry are among the occupational areas in which exposure to vibration is frequent.

Vibration exposure is often concurrent with exposure to dust and noise, both of which are manifest risk factors for myocardial infarction (MI), one of the most common causes of death in Sweden today.

Cardiovascular system

The circulatory system comprises the blood, the vascular system, and the heart, where the latter two are termed the cardiovascular system. The cardiac muscle cells, the myocardium, enables the heart to produce the flow necessary to provide organs and body tissues with needed oxygenated blood through two circuits; pulmonary and systemic circulation. The pulmonary circulation pumps the blood from the right ventricle through the lungs to the left atrium, and systemic circulation pumps it from the left ventricle through the rest of the body organs to the right atrium.

The vascular system is divided into arteries, which leave the heart with oxygenated blood, and veins which redirect blood to the heart. The flow in the vascular system is determined by the blood pressure, the cross-sectional area (contraction and relaxation of vascular smooth muscle) of the arteries/veins and the viscosity of the blood (10, 11).

Regulation

The body must be able to adapt to various physiological demands. This is achieved by allostasis (12, 13), a process that enables physiological stability to be sustained through numerous different regulatory processes. One allostatic-regulated system is the cardiovascular system, which fluctuates in order to meet physiological and mental stress demands. Regulatory systems comprise receptors and effectors, and the processes are nervously and/or chemically (hormones) mediated. Nervously-regulated systems are fast and

Background

specific, while hormones released in the circulatory system can have a more general effect. Important physical functions are regulated by several different systems, usually a combination of nervously and chemically mediated (neuroendocrine).

The autonomic nervous system (ANS) regulates the blood vessels' smooth muscle and cardiac muscle activity (10, 11). The two divisions of ANS, the sympathetic and the parasympathetic, are both part of the neuroendocrine sympathetic adrenal-medullary (SAM) system, and play a major role in the regulation of cardiac rhythm and circulation. Sympathetic activation generally prepares the body for a fight or flight by increasing the heart rate and dilating the airways, while an increase in parasympathetic activity promotes anabolic functions through e.g. increased motility and tone in stomach and intestines, and reduced heart rate (10, 11). In healthy people, parasympathetic effects usually predominate over sympathetic effects, since the former dampens the intrinsic heart rate from about 100 to 70-80 beats per minute.

The parasympathetic nervous system is neural, with the neurotransmitter acetylcholine in both pre- and post-ganglionic synapses. The sympathetic part of the ANS is neuroendocrine with norepinephrine (noradrenaline) as the neurotransmitter, and with secretion of epinephrine (adrenaline) and small amounts of norepinephrine from the adrenal medulla into the blood.

Since the parasympathetic system is regulated neurally, parasympathetic activity results in fast and short-lasting responses. In contrast, the effects of sympathetic stimulation are slower and longer lasting, since the process involves the secretion of hormones into the circulatory system.

Most autonomic effectors are innervated by both sympathetic and parasympathetic nerve fibers, a so-called dual innervation. Where one part has an excitatory effect and the other an inhibitory effect. Thus, an increase in heart rate is an effect of a sympathetic drive as well as a decrease in parasympathetic activity.

In addition to the SAM system, the hypothalamic-pituitary-adrenocortical axis (HPA-axis) is also involved in stress reactions in the body, and they are reciprocally responsible for the physical and mental responses necessary for adaptation to a stressful situation. Sympathetic innervation activates the HPA axis, resulting in secretion of cortisol from the adrenal cortex into the blood. The main function of the HPA axis is to break down energy stored in the liver and muscles in order to provide energy for a fight or flight.

Heart rate, in addition to the combined drive from sympathetic and parasympathetic activity, is also regulated by chemo- and baro-receptors.

Baroreceptors respond to changes in blood pressure with a negative feedback loop, while chemoreceptors react to concentration of O₂ and CO₂ in blood, thereby influencing heart rate (10, 11).

More general physical stress responses, not further described in this thesis, can be measured by blood pressure or assessment of the stress-released hormones cortisol or catecholamines (norepinephrine, epinephrine and dopamine) (10, 11).

Electrocardiogram and Heart-rate variability

Fluctuations in heart rate over time, mirroring cardiac regulation, can be analyzed by recording an electrocardiogram (ECG) and analyzing heart-rate variability (HRV). The ECG represents contraction of myocardial cells, triggered by depolarization of plasma membrane. Initial depolarization arises in the sinoatrial (SA) node, which is the pacemaker for the heart, and leads to contraction of all myocardial cells in the atria. The link between atrial and ventricular contraction, the atrioventricular node, is where the depolarization spreads to the ventricles via fibers, termed bundle of His. The myocardial cells in the SA node manifest spontaneous self-excitation, and the SA node has an inherent rate of approximately 100 contractions per minute. An electrocardiogram (ECG) is recorded from the surface of the body and reflects electrical signals in the myocardium. Typically, the QRS wave is registered, representing excitation of the myocardium of the ventricles.

HRV defines the natural fluctuations in beat-to-beat alterations, and a low variability has been linked to increased cardiac morbidity (14, 15). The method has been widely used over the past few decades, and the two main time frames for registering HRV are long-term (24 h) and short-term (minutes) recordings (16-18). The main methods used for analysing HRV are time domain, geometric methods, and frequency domain analysis (16, 19). It is frequency domain analysis that is relevant for this thesis. R-to-R intervals (from the QRS wave) are registered by a single lead ECG and then converted to frequency domain data by spectral analysis. The power spectrum received is generally presented as total variability (P_{TOT}) as well as being divided into spectral regions. The most common measures are the power density in the very low frequency area, VLF (P_{VLF}), the low frequency area, LF (P_{LF}), the high frequency area, HF (P_{HF}), and the ratio between LF and HF (LF/HF). The frequency regions represent modulations in the sympathetic and parasympathetic components of the

ANS. Roughly, the HF reflects the parasympathetic (vagal) activity, the LF region describes sympathetic activity, fluctuation in the VLF area is associated with changes in peripheral vascular resistance and temperature regulation, and the ratio LF/HF reflects the sympatovagal balance (16, 18).

Exposures

Vibration

Exposure to vibration may be categorized as either local or whole-body vibration (WBV), and the local exposure is usually referred to as hand-arm vibration (HAV). Vibration intensity is measured as acceleration in the SI unit m/s^2 . In Sweden in 2007, an estimated 414 000 (350 000 men, 64 000 women) workers between the ages of 16 and 64 were exposed to hand-arm vibration at work (20). The definition of exposure was answering 'yes' to the question "Are you exposed to vibration from hand held tools for at least 25% of your work time?". The corresponding number exposed to WBV at work in 2007 was approximately 302 000 workers (281 000 men, 21 000 women) who answered 'yes' to the question "Are you exposed to vibrations that make your whole body shake for at least 25% of your work time?" (20). In 2001, approximately 1 million hand-held tools and 800 000 vehicles were used in various occupations in Sweden, with mechanics and construction workers being frequently exposed (21). Measuring and evaluating HAV and WBV is regulated by international standards (22-24), and in 2002, the European Union set out a directive on vibration action and exposure limits for workers (25). This directive has been implemented in Swedish law as of June 2005, with a stated action level of 2.5 m/s^2 for HAV and 0.5 m/s^2 for WBV (8 hours equivalent) (26). The exposure limit values (8 hours equivalent) are set to 5 m/s^2 for HAV and 1.1 m/s^2 for WBV.

In addition to exposure action and limit values, the ISO standard also states the frequency range for measuring and analysing vibration exposure. The frequency range for HAV is 5-1500 Hz, while the corresponding range for WBV is 0.5-80 Hz. For both HAV and WBV measurement and analysis, the frequencies should be weighted in order to correspond to the sensitivity of the body (22, 24).

Noise

Prolonged exposure to high noise levels is associated with permanent damage to the ears, and could result in tinnitus and/or hearing impairment (27). Other health effects studied in relation to noise exposure are annoyance and hypertension (28, 29).

The terms noise and sound often mean the same, but according to the World Health Organisation (1980), noise is generally defined as unwanted sound. The sound level is measured as the amplitude of the sound wave, and is specified in terms of its sound pressure level (SPL). The SPL is measured in the SI unit pascal (Pa), and converted into dB. For risk assessment of noise, a filtered dB, dB(A), is used to represent the sensitivity of the human ear.

As for vibration, an international standard regulates how noise is measured and evaluated, and a European directive lays down occupational exposure limits (30). The Swedish directive on occupational noise exposure states an 8-hour equivalent exposure limit value of 85 dB(A) (31). In 2007 in Sweden, 654 000 men and 341 000 women in work stated that they were exposed to noise levels that hindered them from holding a conversation at a normal level for at least ¼ of their working day (20).

Dust

Research into the health effects of exposure to particulate air pollution has been of interest since the excess number of deaths following the 1952 London Smog (32). Studies have indicated evidence for short- and long-term health impacts such as asthma and cardiovascular effects related to exposure to particles (33-35). The focus was mainly on ambient particulate air pollution, while the health effects of occupational exposure to particles/dust has mainly come to be of interest in the past decade.

Particles measured in the ambient air are divided into an ultrafine, a fine (PM_{2.5}), and a coarse fraction (PM₁₀), based on their aerodynamic diameter, where the cut-off point in size mainly is determined based on the deposition within the upper airways and lungs (36). PM₁₀ is defined as particulate matter that passes through a size-selective inlet with a 50% efficiency cut-off at 10 microns aerodynamic diameter. The corresponding definition for PM_{2.5} is similar, only with a smaller size-selective inlet. The coarse fraction is mainly of mechanical origin, while PM_{2.5} merges mainly from combustion products.

Particle content in air is described by stating the weight of particles per volume air, usually $\mu\text{g}/\text{m}^3$. Consequently, very small particles might be numerous but still only make a minor contribution to the measured particle content. The mean content of particles in air can either be given as the arithmetic mean (AM) or the geometric mean (GM). AM is calculated as a regular, mathematical mean, while GM is achieved by computing the mean of the logarithmic data.

Certain occupations such as mining, baking, and saw-milling involve high levels of exposure to particles/dust. In Sweden in 2007, approximately 701 000 men and 341 000 women answered 'yes' to the question "Can you see or feel the smell of inorganic and/or organic dust at your work place?" (20). Swedish occupational exposure limits vary for different types of dust. For inorganic, respirable dust, defined as having an aerodynamic diameter $< 5 \mu\text{m}$, the limit level is $5 \text{ mg}/\text{m}^3$.

Cardiac effects

Cardiovascular diseases (CVD) are diseases involving the heart and/or arteries and veins, and include cerebrovascular disease, ischemic heart disease (IHD), and hypertension (i.e. high blood pressure). IHD includes disorders that lead to lack of oxygen in the cardiac muscle (ischemia = restriction of blood supply), and the IHD addressed and discussed in this thesis is myocardial infarction (MI).

An (acute) MI occurs when the blood supply to part of the heart is interrupted. This is most commonly due to blockage of a coronary artery caused by atherosclerotic plaques. The resulting ischemia can cause damage to and/or death (infarction) of myocardium.

CVD is the leading cause of death in developed countries. In Sweden in 2005, there were approximately 40 000 (23 000 men and 17 000 women) incident cases of myocardial infarction (37), and in 2006, approximately 9 500 (5 200 men, 4 300 women) died from MI (38). There are over 200 suggested risk factors for MI (39), but the most well-established ones have been attributed to lifestyle factors, e.g smoking, diabetes, hypertension, high blood cholesterol, obesity, and physical inactivity (40). Additional non-modifiable risk factors are heredity, male sex, and age.

Cardiac effects in relation to exposure to vibration, dust, and noise

Acute effects on autonomic nervous function have been reported in conjunction with exposure to vibration, noise and dust (41-43).

Studies have in various ways investigated the hypothesis that vibration exposure is a stressor causing acute and possibly permanent autonomic imbalance, an imbalance that might be due to an increased sympathetic activity or a result of reduced parasympathetic tone. In a review from 2003, Stoyneva and coworkers suggested that exposure to hand-arm vibration caused neural damage to both sensory and autonomic nerves (43), which might play an important role in the pathophysiology of VWF. Autonomic neural imbalance would result in a more general acute physical response, and studies have shown a relation between vibration exposure and increase in blood pressure, increased heart rate, and a tendency to vasoconstriction (3, 44). Japanese studies have found a reduced R-R interval variation among patients with hand-arm vibration syndrome, which the authors interpreted as an indication of a decreased parasympathetic response among these patients (2, 45, 46). This is supported by a Finnish study, where forestry workers with long exposure to chainsaws showed a decrease in HRV compared to those with a shorter exposure time (47). Similar results were published in another Finnish study, where exposure to vibration was negatively associated with HRV (48). In both these Finnish studies, the authors related the negative effect on autonomic nervous function to a stressor effect of vibration exposure (47, 48).

The autonomic imbalance found in previous studies could be an effect of vibration as a stressor in itself, or it could be due to combination with other stressors associated with working with vibrating tools and machines, e.g noise and/or dust. Palmer et al found an increased incidence of hearing impairment among patients with the diagnosis VWF (41), which supports the theory of an increased autonomic response when exposed to vibration. Tzaneva and coworkers investigated acute effects on HRV before, at the onset, and after exposure to noise (95 dB(A)), and found an increased sympathetic response (49).

Several studies have investigated the acute autonomic effect of exposure to dust (50-53). Magari et al studied occupational exposure to particles, and found a negative relation between HRV and increased PM_{2.5}. Pope et al, Liao et al, and Gold et al all studied heart-rate variability in subjects in relation to ambient air pollution. The results from these three studies all showed decreasing HRV with increasing exposure level to particles (PM_{2.5}).

Background

Exposure to noise, as well as to particulate air pollution, has been reported to be a risk factor for myocardial infarction (1, 33, 54, 55). Literature addressing myocardial infarction in relation to vibration exposure is scarce, but some work has been published where exposure to vibration is mentioned as a possible risk factor for ischemic heart disease (56, 57), and a few studies have shown higher prevalences of risk factors, such as high blood pressure, among those exposed to vibration compared to non-exposed (44, 58, 59). Since exposure to vibration, dust, and noise are often concomitant, there is a need for research into the role of vibration exposure in relation to cardiac outcomes.

AIMS

The overall aim of this thesis was to identify any possible short- and long-term cardiac effects of exposure to vibration. The specific aims were:

- To assess the possible risk of myocardial infarction in relation to work entailing exposure to vibration
- To investigate the effects of short-term exposure to hand-arm vibration on cardiac regulation.
- To assess myocardial infarction mortality in a mining industry, specifically in relation to exposure to vibration.

The ethical committees of Stockholm University (91:259) and Umeå University (04-098 and 03-040) approved the studies included in this thesis.

METHODS

Study design

A case-control study design was used in Paper I, with first acute myocardial infarction event as outcome. Information on potential risk factors, with specific questions concerning exposure to vibration, was collected by means of questionnaires, and the risk of myocardial infarction in relation to vibration exposure was studied.

In Paper II, an experimental setup was used, where healthy subjects were exposed to four different conditions, in a randomized order for each subject: 1) vibration only, 2) noise only, 3) both noise and vibration, and 4) no exposure. A continuous ECG was recorded throughout the experimental situation, and different parameters of heart-rate variability were analysed and used as outcome variables.

Papers III and IV were cohort studies, where the outcome was general mortality and specifically mortality from myocardial infarction among men employed in the two iron-ore mines in Kiruna and Malmberget, Sweden.

Paper III deals with general mortality and myocardial infarction mortality compared to a reference population, while Paper IV concentrates on the relation between myocardial infarction mortality and occupational exposure to vibration and dust.

Subjects

In Paper I, the study base comprised all Swedish citizens living in the county of Västernorrland, who were 45–65 years of age during the period March 1993 to March 1995. For this case-control study, cases were defined as first events of acute myocardial infarction, and were identified through coronary and intensive care units within the county of Västernorrland, the hospital discharge register for the same county, and death certificates from the Swedish national register of causes of death. Controls were identified, and randomly selected after stratification for sex, age and hospital catchment area. The study comprised 475 male subjects (218 cases and 257 controls).

The 20 healthy subjects in Paper II were recruited through an advertisement. There were 10 males and 10 females with a mean age of 25.5 years (21-31).

In Papers III and IV, a cohort of employees in Kiruna and Malmberget was defined based on work records kept by the mining company, LKAB.

The cohort included men who had been employed for at least one year some time between 1923 and 1996, who were resident in Sweden on Jan 1st, 1952, and had not emigrated during the follow-up period (-2001). The inclusion criteria were met by a total of 13,621 men and the cohort contained 488,734 person-years. The reference population used for calculating SMRs was the male population in the northern region of Sweden.

Exposure

Exposure assessment

In Paper I, an individualized vibration exposure assessment was conducted based on information from questionnaires concerning occupations and number of years spent in each occupation. Expert estimations of daily exposure time and exposure magnitude were made for each occupation. The assessment was made for both work and leisure time separately and together, and separate assessments were made for WBV and HAV. The estimated vibration value used for statistical analyses was the frequency-weighted, accumulated, lifetime acceleration [$\text{h} \cdot \text{m}/\text{s}^2$]. In analysis, vibration exposure was first treated as dichotomy, i.e. ever vibration exposed as compared to never exposed. Two different exposure groups were compared to a no exposure group; those exposed to HAV only and those exposed to a combination of HAV and WBV. These two groups were treated as both dichotomous and, in order to examine a possible exposure-response relation, were divided into tertiles (low, medium, and high exposure).

For Paper III, the only categorization concerning exposure was defined as “working underground”. This was based on occupational code and time period.

In Paper IV, a job-exposure matrix (JEM) was created for vibration and dust exposure. Exposure assessment for vibration was made based on job title and for eight different time periods. As for Paper I, estimations were made for time and magnitude for all occupations, and separate assessments were made for HAV and WBV. The frequency-weighted 8-hour equivalent acceleration was calculated, and the vibration value used for statistical analyses was the 8-hour equivalent acceleration multiplied by years spent in each occupation, giving the accumulated lifetime acceleration [$\text{year} \cdot \text{m}/\text{s}^2$].

No exposure estimation could be made for eight occupations due to unclear job descriptions. We performed a sensitivity analysis, where instead of the eight occupations set to an acceleration level of $0 \text{ m}/\text{s}^2 \cdot \text{years}$, they

Methods

were set to the mean exposure for all other exposed occupations during respectively time period.

Estimations concerning exposure to respirable dust (<5 μm in diameter) were made based on a total of 1981 dust samples collected between 1968 and 1995 by LKAB. The exposure levels were estimated for two time periods; 1968-1973, and from 1973 onwards. The cut-off at 1973 was because of a reduction in exposure due to the introduction into the mines of mechanical ventilation. The JEM was constructed by safety engineers from the mines and an occupational hygienist (KE), and estimated concentrations [mg/m^3] were multiplied by number of years to achieve cumulative exposure [$\text{years}\cdot\text{mg}/\text{m}^3$].

To assess a possible exposure-response relation, both HAV, WBV and dust were divided into four exposure categories; not exposed, low exposed, medium exposed, and high exposed. The cut-off values for HAV exposure categories were: low exposed >0-30 $\text{m}/\text{s}^2\cdot\text{years}$; medium exposed >30-80 $\text{m}/\text{s}^2\cdot\text{years}$; high exposed >80 $\text{m}/\text{s}^2\cdot\text{years}$. For WBV, the cut-offs were: low exposed >0-2 $\text{m}/\text{s}^2\cdot\text{years}$; medium exposed >2-8 $\text{m}/\text{s}^2\cdot\text{years}$; high exposed >8 $\text{m}/\text{s}^2\cdot\text{years}$. Finally, for dust exposure, the categories were defined as: low exposed: >0-35 $\text{mg}/\text{m}^3\cdot\text{years}$; medium exposed >35-100 $\text{mg}/\text{m}^3\cdot\text{years}$; high exposed >100 $\text{mg}/\text{m}^3\cdot\text{years}$.

Experimental exposure

In Paper II, subjects completed a questionnaire concerning their work environment, general health, medication, hearing and physical activity level. ECG electrodes were attached to the subject, and the test started with the subject resting for 15 minutes while sitting down. For all exposure conditions, the subjects were standing up, gripping the handles, and wearing headphones. Each of the four exposures lasted for 15 minutes and the resting time between the exposures was 30 minutes. The experimental session lasted in total approximately 3 hours.

The vibration exposure was in one direction only with a frequency of 10 Hz and an acceleration level of $5 \pm 0.5 \text{ m}/\text{s}^2$. The feed force was measured and shown to the subjects on an instrument with a pointer to enable them to maintain a constant push force.

The noise exposure was accomplished through headphones, had a frequency spectrum range of 20 to 20000 Hz, and was calibrated for a sound pressure level of $85 \pm 1 \text{ dB(A)}$ at the subject's ear.

Methods

The sampling frequency for ECG was 1000 Hz and the recorded signals were manually inspected and corrected for R-wave detection errors. The R-to-R interval was calculated and converted to a time series by cubic spline interpolation and resampling at 2.4 Hz. The mean heart rate (HR) and the total spectral power (P_{TOT}) were calculated, as well as the spectral power of the frequency components VLF (P_{VLF} , <0.04 Hz), LF (P_{LF} , 0.04-0.15 Hz), and HF (P_{HF} , 0.15-0.4 Hz). LF/HF was also calculated.

Statistics

In Paper I, a randomized, complete-block design was used with three repeated measure averages representing three consecutive 5-min periods nested within each of the four exposure conditions. Analyses were made using General Linear Model (GLM) repeated measurements, with the response variables HR, P_{TOT} , P_{VLF} , P_{LF} , P_{HF} , and the ratio LF/HF. Overall tests were made for condition, time and interaction between condition and time. When different exposures were compared, p-values were adjusted according to Holm's method, to compensate for multiple testing.

In Paper II, estimates of relative risks were based on odds ratios from binary logistic regression. Exposure was analysed dichotomously and as categorized in low, intermediate and high exposure. Odds ratios were adjusted for the potential confounding variables age, smoking, hypertension, diabetes, and obesity.

In Paper III, standardized mortality ratios (SMRs) were calculated for four mortality groups, using the male population in the northern region of Sweden as the reference population. SMRs were also calculated for surface vs underground work and for three strata based on number of years working underground. A Poisson regression model was used to estimate exposure-response relation between mortality and time working underground. For myocardial infarction mortality, analyses were made for two separate age groups, one that represented working age (≤ 60 years) and one post-retirement group (>60 years).

In Paper IV, Poisson regression was used to calculate relative risks (RRs) for myocardial infarction mortality in relation to exposure to vibration and dust. The number of deaths was used as a dependent variable and the logarithm of the person-years as offset. The RRs were adjusted for calendar year period and age. In this paper, as well as in Paper III, analyses were made separately for the two age groups ≤ 60 years and >60 years.

In an attempt to investigate whether risk was related more to an acute than a cumulative effect of exposure, we analysed the risks of MI in relation to exposure during the last year as well as in the last five years during the follow-up period.

RESULTS

A summary of main results from each study are presented below

Paper I

Myocardial infarction incidence in relation to vibration exposure

The case-control study comprised 475 male subjects (218 cases and 257 controls) The overall odds ratio (OR) for contracting myocardial infarction if ever exposed to vibration, either HAV and/or WBV, was 1.6 (95% CI: 1.1-2.4).

Tables 1 and 2 show ORs for contracting MI in relation to accumulated lifetime vibration for the two exposure groups HAV only (Table 1) and combined exposure to HAV and WBV (Table 2), respectively. Exposure to HAV increased the OR by approximately 40 % while exposure to both HAV and WBV increased the risk of MI by more than 80 % (Table 2), but no exposure-response relation was evident.

Results

Table 1. Odds ratios (OR) for myocardial infarction (MI) in relation to accumulated lifetime exposure ([h*m/s²]), divided into tertiles, for the groups exposed to only HAV.

	n		OR [†]	95% CI
	Cases	Contr.		
Only HAV exposed				
Non-exp	59	102	1	
Low	21	20	1.67	0.79-3.53
Medium	19	23	1.63	0.78-3.40
High	16	29	0.99	0.48-2.05
Overall risk of MI, regardless of exposure level	56	72	1.38	0.83-2.28

[†]OR adjusted for overweight, hypertension, smoking, diabetes (type II), hospital catchment area and age.

Table 2. Odds ratios (OR) for myocardial infarction (MI) in relation to accumulated lifetime exposure ([h*m/s²]), divided into tertiles, for the groups exposed to both HAV and WBV.

	n		OR [†]	95% CI
	Cases	Contr.		
HAV&WBV exposed				
Non-exp	59	102	1	-
Low	36	33	1.82	1.00-3.32
Medium	43	36	2.00	1.13-3.55
High	15	13	1.47	0.63-3.46
Overall risk of MI, regardless of exposure level	94	82	1.84	1.16-2.90

[†]OR adjusted for overweight, hypertension, smoking, diabetes (type II), hospital catchment area and age.

Paper II

Acute effects on cardiac regulation

All subjects were analysed together, since we found no gender differences. When testing exposure condition, there was an effect on all HRV parameters except HR, which led to further analysis of which exposure(s) caused the difference(s). Compared to no exposure, total heart rate variability (P_{TOT}) was lower during exposure to vibration than exposure to noise. Compared to the control condition, the variables P_{VLF} , P_{LF} and P_{HF} were all reduced during vibration exposure, and the same variables were all increased during exposure to noise. A combined exposure to vibration and noise significantly reduced variability for the parameters P_{TOT} , P_{VLF} and P_{HF} compared to exposure to noise alone. Combined exposure to vibration and noise increased the ratio LF/HF compared to noise and vibration exposure separately. The ratio LF/HF was essentially of the same magnitude for vibration, noise, and no exposure. HR was the only variable with a significant time effect, with an increasing HR over exposure time. Since the increase was similar for all four exposure conditions, no further analysis was made. Table 3 displays the mean value (for each exposure period) for each HRV parameter and different exposure condition. The superscripts indicate where there was a significant difference between exposure conditions.

Table 3. Mean values (s.d) for the output variables for each exposure type respectively. The superscripts indicate where there is a significant difference between groups (on 95% confidence level).

Output Variable	Experimental Condition			
	Vibration	Noise	Combined	No Exposure
HR	87.3	83.2	86.1	84.5
P_{TOT}	3.76 ^{N,0}	3.94 ^{V,C,0}	3.77 ^N	3.87 ^{V,N,C}
P_{VLF}	3.34 ^{N,0}	3.59 ^{V,C}	3.36 ^N	3.51 ^{VC}
P_{LF}	3.43 ^N	3.56 ^V	3.47	3.50
P_{HF}	2.48 ^N	2.62 ^V	2.45 ^N	2.57 ^C
LF/HF	0.94 ^C	0.94 ^C	1.02 ^{VN}	0.93

V=vibration, N=noise, C=combined exposure to vibration and noise, 0=no exposure

Paper III

Myocardial infarction mortality in a mining industry

During the 50-year follow-up period, there were a total of 4504 deaths (from all causes) in the cohort. This corresponded to an SMR of 1.05 (95% CI 1.02-1.09). The SMRs were increased for the main mortality groups ‘injuries and poisonings’ (SMR 1.34, 95% CI 1.24-1.46) and ‘respiratory diseases’ (SMR 1.14, 95% CI 1.00-1.28). There were 1477 cases of myocardial infarction, which corresponded to an SMR of 1.12 (95% CI 1.07-1.18) (Table 4). The SMR was higher for the age group less than or equal to 60 years than for that above 60 years. There was no increased relative risk connected with underground work compared to surface work for either age group or for all men.

Results

Table 4. Standardised Mortality Ratio (SMR) for myocardial infarction for all workers (total), surface workers, underground workers, and underground workers subdivided into number of working-years underground. Comparison of mortality rates (relative risks, RR) between surface and underground workers (surface vs underground) and for number of years of working underground are based on Poisson regression.

Age	Total			Surface work			Underground work			Surface vs underground			Underground work by number of years*		
	n	SMR (95% CI)	n	SMR (95% CI)	n	SMR (95% CI)	SMR (95% CI)	n	SMR (95% CI)	RR (95% CI)	n	SMR (95% CI)	RR (95% CI)		
≤ 60 years	371	1.35 (1.22-1.50)	115	1.47 (1.21-1.76)	256	1.30 (1.15-1.48)	0.89 (0.71-1.01)	0-5	88	1.21 (0.97-1.50)	1	1	1		
								5-15	84	1.23 (0.98-1.52)	1.02 (0.75-1.37)				
								>15	84	1.51 (1.21-1.87)	1.25 (0.93-1.68)				
> 60 years	1106	1.06 (1.00-1.13)	307	1.02 (0.91-1.14)	799	1.08 (1.00-1.16)	1.06 (0.93-1.21)	0-5	189	0.97 (0.83-1.11)	1	1	1		
								5-15	272	1.10 (0.97-1.23)	1.13 (0.94-1.37)				
								>15	338	1.14 (1.02-1.26)	1.18 (0.98-1.40)				
Total	1477	1.12 (1.07-1.18)	422	1.11 (1.01-1.22)	1055	1.13 (1.06-1.20)	1.02 (0.91-1.14)	0-5	277	1.03 (0.92-1.16)	1	1	1		
								5-15	356	1.13 (1.01-1.25)	1.10 (0.94-1.28)				
								>15	422	1.20 (1.08-1.32)	1.17 (1.00-1.36)				

*Cumulative employment time.

Paper IV

Myocardial infarction mortality in a mining industry in relation to vibration and dust exposure

Relative risks of MI mortality related to exposure to HAV, WBV or dust univariately showed that in the age group ≤ 60 years, both HAV (RR: 1.34) and WBV (RR: 1.39) exposure significantly increased the risk of MI mortality (Table 5). Neither of the exposure types significantly increased the risk of MI mortality in the over-60-years group.

In the younger age group there was an exposure-response relation, where medium and high exposed categories for HAV, WBV and dust exposure all showed a significantly increased risk.

Table 6 show RRs for HAV and WBV adjusted for dust exposure. There was a significantly increased risk estimated for WBV >0 in the younger age group. There was no increased risk related to exposure among the older age group.

Table 7 shows relative risks of myocardial infarction mortality in relation to occupational exposure for the past year or five years of follow-up. No increased RRs and no exposure-response relation were found.

Results

Table 5. Relative risks (RR) with 95 % CI of myocardial infarction mortality in relation to cumulative exposure to hand-arm vibration (HAV), whole-body vibration (WBV), and dust estimated separately. RRs are shown for separate exposure categories and with respect to attained age.

	Attained age ≤ 60 years			Attained age > 60 years		
	N	RR	95% CI	n	RR	95% CI
exposure categories						
HAV[†]						
Not exposed	68	1	-	235	1	-
Low	134	1.03	0.77-1.39	302	0.94	0.80-1.12
Medium	110	1.82	1.34-2.46	272	0.93	0.78-1.11
High	59	1.71	1.20-2.46	297	0.98	0.83-1.17
HAV>0	303	1.34	1.03-1.74	871	0.95	0.82-1.10
WBV[‡]						
Not exposed	145	1	-	415	1	-
Low	79	1.18	0.90-1.56	204	0.99	0.84-1.17
Medium	82	1.51	1.15-1.98	280	1.16	0.99-1.35
High	65	1.59	1.18-2.13	207	1.07	0.91-1.27
WBV>0	226	1.39	1.13-1.72	691	1.08	0.95-1.22
Dust[‡]						
Not exposed	89	1	-	222	1	-
Low	114	0.93	0.71-1.23	247	1.04	0.87-1.25
Medium	85	1.36	1.01-1.84	270	1.12	0.94-1.34
High	83	1.82	1.33-2.49	367	1.16	0.98-1.37
Dust>0	282	1.21	0.95-1.53	884	1.11	0.96-1.29

[†]: unit m/s²*years, [‡]: unit mg/m³*years

Results

Table 6. Relative risks (RR) with 95 % CI of myocardial infarction mortality in relation to cumulative exposure to whole-body vibration (WBV) and hand-arm vibration (HAV), adjusted for dust exposure. RRs are shown for separate exposure categories and with respect to attained age.

Cumulative exposure categories	Attained age ≤ 60 years			Attained age > 60 years		
	n	RR	95% CI	n	RR	95% CI
HAV[†]						
Not exposed	68	1	-	235	1	-
Low	134	1.06	0.78-1.43	302	0.94	0.78-1.12
Medium	110	1.68	1.21-2.32	272	0.89	0.74-1.07
High	59	1.31	0.87-1.98	297	0.89	0.74-1.08
HAV>0	303	1.29	0.98-1.70	871	0.91	0.78-1.06
WBV[†]						
Not exposed	145	1	-	415	1	-
Low	79	1.20	0.89-1.61	204	0.97	0.81-1.16
Medium	82	1.40	1.03-1.91	280	1.11	0.94-1.32
High	65	1.29	0.91-1.83	207	1.02	0.85-1.23
WBV>0	226	1.39	1.09-1.78	691	1.04	0.91-1.20

†: unit $m/s^2 \cdot years$

Discussion

Table 7. Relative risks (RR) with 95 % CI of myocardial infarction mortality in relation to vibration exposure during the past one and five years of follow-up respectively. RRs are shown for whole-body vibration (WBV), hand-arm vibration (HAV) and dust exposure respectively, and for separate exposure categories.

Exposure categories	Exposure last year of			Exposure last five years of		
	n	RR	95% CI	n	RR	95% CI
HAV [†] = 0	109	1	-	95	1	-
>0-2	42	0.86	0.60-1.23	47	0.72	0.51-1.03
>2	50	1.13	0.80-1.60	59	1.27	0.91-1.77
HAV>0	92	0.99	0.75-1.30	106	0.94	0.71-1.25
WBV [†] = 0	156	1	-	138	1	-
>0-0.5	19	0.72	0.45-1.16	35	0.87	0.60-1.27
>0.5	26	1.16	0.77-1.76	28	1.24	0.83-1.87
WBV>0	45	0.92	0.66-1.29	63	1.01	0.75-1.36
Dust [‡] = 0	109	1	-	87	1	-
>0-2	51	1.13	0.80-1.60	62	1.12	0.81-1.56
>2	41	0.72	0.49-1.07	52	0.92	0.64-1.32
Dust>0	92	0.92	0.69-1.22	114	1.03	0.78-1.36

[†]: unit m/s²*years

[‡]: unit mg/m³*years

DISCUSSION

In this thesis, acute and long-term cardiac effects in relation to vibration exposure were investigated. In the case-control study, the odds ratio for myocardial infarction was 1.6 among workers ever exposed to either HAV and/or WBV compared to non-exposed. The results showed no exposure-response when the vibration exposure was analysed in tertiles. The group with combined exposure to both HAV and WBV not only had a higher risk estimate (OR=1.8 vs OR=1.4), but also had a higher accumulated vibration exposure than those exposed only to HAV. This could, therefore, be interpreted as an exposure-response relation.

The results from the experimental study indicated an acute effect on autonomic cardiac regulation with exposure to either vibration or noise or both simultaneously. Total HRV decreased during vibration exposure and increased with exposure to noise, indicating either an increased sympathetic drive or parasympathetic activity. The results of the combined exposure to vibration and noise were similar to those for exposure to vibration only, which suggests that vibration has a stronger impact on acute autonomic effects than noise.

Two of the papers are based on analyses of a cohort of iron-ore miners in Kiruna and Malmberget, Sweden. There was an increased myocardial infarction mortality compared to the reference population (SMR=1.12). The relative risk of myocardial infarction mortality was increased overall for exposure to WBV and dust separately and dichotomously (0/>0). At working age, relative risks were increased for HAV and WBV, with an exposure-response tendency, while none of the exposures significantly increased the risk of MI mortality for the age group older than 60 years. The relative risks of MI mortality remained for exposure to WBV after adjusting for dust exposure, both totally as well as in the working-age group.

Myocardial infarction risk

We found an increased risk of MI in the cohort of iron-ore miners compared to a reference population. When looking at the two age groups, only the group who were younger than 60 years had a significantly increased SMR. Neither of the age groups revealed a significantly higher risk in conjunction with underground work compared to surface work. There was, however, a tendency for the risk to increase with increasing number of years spent working underground, although the separate risk estimates were not statistically significant. The increased MI mortality among employees in the mine is supported by results from a cohort study in a copper and zinc mine, where an increased number of deaths from ischemic heart disease was found (60). In addition, increased ischemic heart disease mortality has also been found in a Swedish cohort of workers exposed to silica. Some of the subjects included were miners (61).

The results from the case-control study showed an increased risk of myocardial infarction for subjects ever exposed to either HAV and/or WBV. The overall risk estimates in Paper IV, for the corresponding age group, also suggest an increased risk of MI when exposed to HAV or WBV. The results from Papers I and IV are presented for different outcomes, since Paper I has

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fatal as well as non-fatal first event MI as an outcome, while paper IV deals only with mortality from MI. However, the results point in the same direction.

In Paper I, subjects exposed to HAV only were separated from those with exposure to both HAV and WBV. The former group had lower cumulative vibration exposure than those with combined exposure. Since the group exposed to HAV only had a lower OR than the combined exposure group, this was interpreted as being a rough exposure-response relation. However, no clear exposure-response HAV or HAV and WBV respectively was found when comparing low, medium, and high exposed groups. For combined exposure to HAV and WBV, the medium exposed group had a significantly doubled risk of MI, while the risk for the high exposed group was not significantly increased.

The exposure-response relations were clearer in Paper IV, where there was a tendency among the working-age group towards increased risk estimates for MI among medium and high exposed for both HAV and WBV. Neither HAV nor WBV had an increased RR in the low-exposed groups, which implies that a certain cumulative dose is needed for an increased risk. When the RRs for MI in relation to vibration exposure were adjusted for dust exposure, these results remained only for WBV among the working-age group. The risk estimate for medium exposure to WBV for ≤ 60 years remained significantly increased, but not among the high-exposed group. This was in line with the results from Paper I, where the medium-exposed groups had an increased risk while the high-exposed groups did not. In both cases, the high-exposed groups had about half the number of cases/MI mortalities, making the risk estimates for the high-exposed groups less reliable.

The mean HAV exposure in the category low-exposed would correspond to an equivalent daily exposure at the action level of 2.5 m/s^2 for 6 years, while the mean exposure in the high-exposed group would correspond to an equivalent daily exposure of 5 m/s^2 for 16 years.

As scientific work specifically addressing the relation between vibration exposure and the outcome of myocardial infarction is scarce, it is difficult to find results which to relate our statistics. However, there are studies that suggest an increased occurrence of risk factors for MI, such as high blood pressure, among those exposed to vibration (44, 58).

Exposure to particles has been reported earlier as a risk factor for cardiovascular morbidity and mortality (62-64), and two main possible pathomechanistic explanations have been proposed. One is that the risk

might be mediated by an inflammatory effect (65, 66), and the other that a disturbance arises in the autonomic nervous system due to exposure (53). In Paper IV, myocardial infarction mortality in relation to dust exposure was increased for all participants. There was a significantly increased MI mortality among medium and high exposed in the working-age group, although MI mortality in relation to total, dicotomous (0/>0) dust exposure was not significant despite an increased risk estimate. This could be due to the higher number of MI cases among the low-exposed group. The results concerning MI in relation to dust exposure are in agreement with earlier literature, where Torén et al found an increased mortality from IHD among construction workers (20-59 years of age) occupationally exposed to dust (64).

The low-exposed dust group did not show an increased risk estimate for MI mortality. Possible explanations for this might be that a certain cumulative dose is needed for an increased risk or that the measured fraction of the particles (<5 µm) was too coarse. There are studies which show an association between cardiovascular mortality and exposure to smaller particles (67-69).

In Paper I, several of the occupations involved exposure to exhaust and/or particles as well as to vibration. We performed no exposure assessment for dust, and thus this could thus not be controlled for.

Acute cardiac effects

There was an acute effect on the ANS during exposure to vibration and during combined exposure to vibration and noise. This was shown as a reduced total variability (P_{TOT}), which in previous work has been found to be a marker of reduced parasympathetic activity (16, 70). Previous work by Heinonen et al found an independent, negative association between number of years working with chain saws and total HRV, which was interpreted by the authors as a negative effect on parasympathetic activity caused by vibration exposure (48). Laskar et al support the results of Heinonen et al, as they found reduced parasympathetic activity in patients with hand-arm vibration syndrome in comparison with healthy controls (71). Thus, the reduced total heart-rate variability found in Paper II could reflect a reduced parasympathetic autonomic modulation. In addition to results indicating a reduced parasympathetic activity, there are also studies which suggest that patients with hand-arm vibration syndrome have a greater sensitivity of the sympathetic nervous system (72, 73). Our findings suggest that there is a

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greater negative effect on parasympathetic activity during acute exposure to vibration than to noise, since the P_{HF} was significantly lower for exposure to vibration only than for noise only. A disturbance in the ANS for those exposed to vibration and noise is supported by Palmer et al. In their study, they found an increased risk of severe hearing loss among subjects with Raynaud's phenomenon (41).

The autonomic balance, measured by the LF/HF ratio, remained unchanged during exposure to vibration only and noise only compared to no exposure. The ratio was significantly increased for combined exposure to vibration and noise compared to the single exposures respectively. The unchanged ratio might be explained by a concurrent reduction in sympathetic modulation and parasympathetic activity, while the increased ratio resulting from combined exposure could reflect either increased sympathetic activity or a reduction in parasympathetic activity.

During exposure to noise, the total variability increased, i.e. the effects were the opposite of those from exposure to vibration only. A negative health impact from exposure to noise is supported by earlier work (74). van Amelsvoort et al interpreted their results as an increased sympathetic activity among a group of workers exposed to high noise levels as opposed to those exposed to low levels. This is supported in Paper II, where P_{LF} was significantly higher during noise exposure than during vibration exposure. However, although the measure P_{LF} is considered to reflect sympathetic activity, the frequency area covered by P_{LF} also includes influences from parasympathetic activity (16). Contrary to the results in Paper II, Yanagihashi et al found acute decreased parasympathetic activity during exposure to mechanical noise compared to music and/or birds song (75). However, the sound level was freely selected for the subjects for the different types of noise exposures, which makes it difficult to compare with our work.

Although exposure to noise resulted in an increment of total variability, combined exposure to vibration and noise resulted in a reduction of the same. This indicates that vibration influences HRV more strongly than noise.

Papers I and IV both include risk estimates for cumulative exposure to vibration. In both papers, we attempted to make analyses based on more 'acute' exposures than accumulated lifetime exposure. In the case-control study, analyses were made based on vibration exposure in the 12 months preceding inclusion in the study, and the risk estimates were similar for

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those of accumulated lifetime exposure. One possible explanation might be that the subjects exposed during the past year before inclusion had also been exposed before, making it difficult to discriminate between exposure assessments. An alternative way of interpreting the results could be to consider an exposure assessment focused mainly on recent exposure to be as good as a more complete assessment over an entire work period.

In analogy with ideas in Paper I, risk estimates for MI mortality in Paper IV were calculated in relation to exposure during the last year and five years respectively of the follow-up period. The results showed no individually increased RRs for HAV, WBV or dust, and there was no exposure-response relation. However, results show that most cases of MI mortality were collected during the last year of follow-up, and the preceding 4 years did not contribute greatly to the number of cases. For instance, for the higher HAV-exposed group, the last year of follow-up included 50 cases, while the preceding 4 years only added 9 cases. This could be interpreted as a tendency for the effect to depend more on recent exposure than an accumulated lifetime exposure.

We used the same cut-off exposure doses for the two 'time-frames' one year and five years. None of the vibration doses was as high as the medium-exposed group's calculated for the whole follow-up period, i.e. cumulative medium exposure. These results could be interpreted as showing that not only might the time-frame be of interest, but it might also be necessary to exceed a certain dose before becoming at risk.

Patients with hand-arm vibration syndrome have been found to show greater negative effects on HRV compared to healthy subjects (71). The possible pathomechanism by which exposure to vibration affects the cardiac system through acute autonomic regulation is analogous with theories discussed in relation to the acute effects of particles (42, 76). It has previously been shown that vulnerable groups, i.e. groups with reduced autonomic regulation, such as diabetics, the elderly and individuals with hypertension, are more affected to exposure to ambient particles (76). In line with that discussion, one might speculate that vibration exposure, as well as exposure to particles, among more vulnerable groups could trigger an effect, leading to an infarction.

Additional possible risk factors for myocardial infarction

Risk factors for myocardial infarction, as previously mentioned, are most frequently studied in relation to individual factors such as BMI, high blood pressure, smoking, age, and sex. The effects of these factors are only partly controlled for in this thesis, as follows. The results for myocardial infarction in Papers I, III, and IV all concern male subjects, and the SMRs, ORs, and RRs were adjusted for age. In Papers III and IV, the analyses were made on separate age groups to show the risk at working age, but the figure were still adjusted for age. The acute effects in Paper II did not differ between the sexes and all the subjects were young and healthy.

In the case-control study, smoking was controlled for in the analysis, while the cohort studies only included information on smoking for a subgroup of employees (n=3,831). The information was obtained from health examinations during the 1980s, and the proportion who smoked in the cohort was compared to the proportion of smokers in the general population in Sweden. There was a 1.6% higher proportion of smokers in the cohort compared to the general Swedish population. Due to the decrease in the number of smokers between 1980 and 1989, the overestimation was approximately 2%. Thus the data do not support the view that the increased risk of MI might be attributable to a higher proportion of smokers in the cohort than in the general Swedish population. However, the results in Papers III and IV were never adjusted for smoking. There were no smokers and only 3 used snuff among the subjects in Paper II. The nicotine users were asked not to smoke/take snuff for at least 2 hours before the test. The effect of nicotine use should thus not be an issue in Paper II.

In a recent case-control study covering 52 countries, the authors found an association between BMI and MI, but an even stronger relation between the anthropometric measure waist-to-hip ratio and MI (77). The results in Paper I were adjusted for obesity (BMI \geq 30), but this was not possible in Papers III and IV. The level of mortality in Paper III was compared with that in the general male population in the northern region of Sweden. During the period 1986-2004, the proportion of men in the male population of Norrbotten and Västerbotten with a BMI \geq 30 doubled, although myocardial infarction mortality decreased by 8% per year between 1985 and 1994 (78). There is no reason to suspect an increased occurrence of obesity among miners compared to the reference population in Paper III, and in Paper IV, the employees within the cohort were compared amongst themselves.

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The results in Paper I were adjusted for hypertension, while no such adjustment was possible in Papers III or IV. Since previous studies have found an increased incidence of high blood pressure (44) among those exposed to vibration, an adjustment for hypertension might result in an underestimation of the risk of exposure to vibration. This is supported by results that imply an association between vibration exposure and effects on the autonomous nervous system (79, 80), which could give rise to changes in blood pressure.

Vibration and dust exposure are both physical stressors and the results in this thesis and in earlier work indicate that they have an effect on the SAM system. This also induces an effect on the HPA-axis, and one suggested pathomechanistic way to increased myocardial infarction risk might lie in the wear and tear on the allostasis, i.e. allostatic load. A work situation that is mentally stressful also affects the allostasis via the SAM and HPA, thereby potentially increasing a cardiac effect from vibration and/or dust. However, this has not been studied or addressed in this thesis.

Workers in occupations involving exposure to vibration, dust, and/or noise are mainly blue-collar workers from lower socioeconomic or less educated groups. Previous studies have linked higher risk of myocardial infarction to lower social class (81, 82). In Paper I, we had information about socioeconomic status, but it was not included in the regression analyses because both cases and controls changed several times between blue- and white-collar work during their occupational careers. The increased risk for individuals in lower a social class might be due to the lower socioeconomic group itself, or to a higher prevalence of individual risk factors among lower social classes. Examples of such individual risk factors are smoking, high blood pressure, increased BMI, and stress; all of which are discussed above.

Occupation environmental factors with a documented relation to an increased risk of MI often or even always present concomitantly with vibration exposure are noise and shift work (54, 83, 84). Several of the occupations in Paper I and the majority of occupations in Paper IV involve such exposures. The outcome of CVD in relation to noise exposure has been focused mainly on traffic noise (85, 86), which means that the increased risk of CVD due to high noise exposure could be an effect of exposure to high levels of engine exhaust and fine particles in trafficked areas. In line with this discussion, Hammar et al published results showing that metal workers were in one of the occupations at highest risk of MI. Since metal workers were the most common vibration-exposed occupation group in Paper I, the

findings of Hammar et al might be a result of high vibration exposure. An occupation group found to be at risk of IHD due to occupational exposure to particles is construction workers (64). Construction workers is also one of the occupations most exposed to vibration in Paper I. Thus, exposure to vibration, dust, and noise are often concomitant and it is difficult to separate the effects of the one from the other.

Neither of the risk estimates in Papers I or IV has been adjusted for the possible confounder noise, but the results in Paper IV imply that an increased risk of MI associated with WBV remains after adjustments were made for dust exposure.

Methodological considerations

Papers I and IV both contain retrospectively created exposure matrixes. The approximations needed to do this are not likely to create misclassification within the exposure categories. The exposure assessments are based on earlier measurements and documentation of vibration and dust levels. In Paper IV, these were all done prospectively, and thus the misclassification is not dependent on outcome. Such non-differential misclassification would indicate an underestimation of risk estimates due to vibration, but a possible misclassification of dust exposure could lead to an overestimation of risk due to vibration. In Paper I, the exposure assessments were made for all individuals, based on self-stated information from questionnaires on occupations, number of years spent in each occupation, and specific questions about exposure to vibration. The information collected may be influenced by recall bias, since overestimation can be a problem with retrospective information. However, since vibration exposure is not an established risk factor for MI, there is no reason to believe there is a discrepancy in recall bias between cases and controls, and thus no influence on the calculated ORs.

Exposure level was estimated at work level, and only one estimation of exposure was made per type of machine. This can vary both within one machine and between different machines of the same type. The same is true for the workers, who could have two separate work days with various exposures within the same occupation. The vibration exposure matrix in Paper IV was based only on occupation code, and thus all drillers, for example, were estimated to have the same exposure level, although it is likely that variation within this occupation is large.

Discussion

In Paper IV, it was not possible to separate the HAV exposure from the WBV exposure. In order to try to estimate the risk of MI if ever vibration exposed to either HAV and/or WBV, the HAV and WBV variables were 'normalised' and added into a variable with total vibration. The results from this analysis showed a significantly increased RR for the miners of working age, which was remained after adjustment for dust exposure. This risk estimate was higher than the separate risk estimates for HAV and WBV respectively.

In Paper II, young, healthy people were exposed as opposed to other HRV studies which mainly compare autonomic regulation between healthy subjects and subjects with hand-arm vibration syndrome. The main purpose of the experimental study, however, was not to be able to generalize the results to an exposed population, but to examine a possible pathomechanism. The exposure levels for hand-arm vibration and noise were comparable to a possible occupational situation. The exposure time lasted a total of 30 minutes, which would correspond to an 8-hour equivalent vibration value of about 1.3 m/s^2 , i.e. considerably lower than the action level.

CONCLUSION

The studies comprised in this thesis demonstrate:

- Work entailing vibration exposure is a risk factor for myocardial infarction.
- Short-term exposure to hand-arm vibration produces an acute effect on autonomic cardiac regulation compared to being without exposure. Exposure to vibration generated a decrease in total heart rate variability.
- Mortality from myocardial infarction was increased in the studied cohort, and the increment was higher for those younger than 60 years. The working-age group had an increased MI mortality attributed to exposure to vibration.

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