



Cardiovascular Reflexes in Monozygotic Twins Discordant for Exposure to Organic Solvents

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Abstract. Eighteen pairs of monozygotic twins discordant for long-term occupational exposure to organic solvents were examined for disturbances of cardiovascular reflexes. All of the subjects were asymptomatic, and considered themselves healthy. No significant differences were observed between the exposed and the nonexposed twins. The finding suggests that occupational solvent exposure at these particular levels is unlikely to cause disturbances of the autonomic nervous function.

Key words: Neuropathy, Solvent exposure, Cotwin control study

INTRODUCTION

The main target of many neurotoxic solvents in occupational settings is the central nervous system of the exposed subject. Peripheral neuropathy is more uncommon, although it has been demonstrated after heavy exposure to chemicals such as n-hexane, methyl-n-butyl ketone, and carbon disulfide [1,5]. There are also reports of slight peripheral neuropathy in solvent intoxications caused by commonly used mixtures of solvents, in which the effect of individual solvent may be difficult or entirely impossible to measure [4].

Disturbances of the autonomic nervous system have been described in many diseases associated with peripheral neuropathy [11]. These include diabetes mellitus, renal insufficiency, paraneoplastic neuropathy, chronic alcoholism, and some other diseases. In a previous study we have described impaired function of autonomic reflexes in a group of workers occupationally exposed to organic solvents [9]. These were all symptomatic patients, who had been remitted for further examinations to the Institute of Occupational

Health, Helsinki, Finland. In all these cases the exposure had lasted for several years (mean 16.2 years). The abnormalities in autonomic function were concentrated in the parasympathetic division. The findings were most evident in workers exposed to carbon disulfide, although the small size of this group prevented further speculations. Otherwise, workers with exposure to solvent mixtures had abnormally low values, whereas those exposed to toluene had normal values. In another study of workers exposed to industrial toluene, we could not find any abnormalities in the functions of the autonomic nervous system [6]. However, studies of this kind suffer from biases, such as selection, inadequate referents, etc. To eliminate the effects of inadequate referents, we chose to study monozygotic twins who were discordant as regards exposure to neurotoxic solvents, but concordant in other respects. This allows us to observe the effect of the discriminating factor with greater accuracy.

PATIENTS AND METHODS

The subjects participating in the study came from the Finnish Twin Cohort (FTC), which is a data-base consisting of all Finnish twins, both monozygotic (MZ), and dizygotic (DZ). The population-based character of FTC makes it possible to study a representative sample of twins, discordant to some factor, avoiding the problems of representativeness in other twin studies, based on non-population-based cohorts. Of all the 3500 MZ twins of FTC, 200 pairs of possible exposure to solvents emerged after preliminary analysis of the recorded data. Of these, 60 twin pairs were picked up after a careful analysis of the exposure data. A questionnaire was sent to all of these twins, and 18 pairs of MZ twins with highest possible discordance to solvent exposure were selected for the study. These twins were evaluated using several sensitive techniques, and in part this evaluation is still continuing. Results of the function tests of the autonomic nervous system of 18 twin pairs are presented here.

All of the patients were fully informed about the study, and all gave their informed consent.

Exposure

All of the subjects were asymptomatic, healthy workers. Nine pairs were women, nine were men. The mean age of the exposed subjects was 43 years (range 28-66 years). The duration of the exposure ranged from 3 to 23 years (mean 13.5 years). The calculated mean exposure index was 4.3 (hygienic standard years), ranging from 0.3 to 12.9. The mean long-term average exposure level was 40% (range 10-100%). For statistical purposes each exposed twin was classified into one of the three exposure categories according to the general level of exposure.

Cardiovascular Measurements

Measurement of cardiovascular reflexes was used to study the function of the autonomic nervous system. The examination was performed in a quiet room with constant humidity and temperature. All of the measurements were made in an identical way for all of the subjects of the study, according to the protocol used in our laboratory. Before each measurement the patient was allowed to rest for a short period of time. Peak-to-peak

variation of the heart rate (HRV), Valsalva manoeuvre, and reactions of pulse and blood pressure to postural change and isometric work were measured.

Variation of the heart rate was measured both during rest, and during maximal deep 6-8/min breathing. The recordings were made using electrocardiographic chest electrodes connected to a heart monitor, which gave a square pulse wave at each QRS-complex. The signal was digitized and read by a microcomputer, and the parameters described below were calculated from the intervals. The results of the measurements were stored for further processing. The parameters of HRV used were the standard deviation (SD) of mean R-R interval, the mean square successive difference (MSSD), percentage of variation from mean (Var %), as suggested by several authors [2,3,12]. The result of the Valsalva manoeuvre was calculated as described by Levin [7] as Valsalva ratio. The postural pulse reaction was recorded during active rise from supine to prone position. The blood pressure change was recorded simultaneously. The ratio between the longest and the shortest R-R-intervals after rising was calculated and used to reflect the postural pulse change. In addition, the subjects were given a detailed and standardized neurological examination, in which particular emphasis was paid to subjective symptoms referring to autonomic disturbances.

Referents

Twenty-six healthy, nonexposed MZ twin pairs (52 subjects) were used as referents for the results of the autonomic nervous system functions. Their mean age and sex distribution were identical to those of the twin group under study.

RESULTS

The results of the measurements of cardiovascular reflexes are shown in the Table. The differences between the mean values of the exposed group and the nonexposed groups were not consistent, and not statistically significant. The differences within each twin pair were also similar among the exposure-discordant twins and the referent twins. The percentage of difference in heart rate variation between the twins of each pair, expressed as standard deviation of the mean heart rate, was 9.8 among the exposed/nonexposed

Table - Mean values of cardiovascular parameters

Parameter	Exposed twins (N = 18)	Nonexposed twins (N = 18)	Referent twins (N = 52)	Probability
SD/normal	40.9 ± 17.5	39.8 ± 15.1	41.3 ± 17.0	NS
Var %	4.96 ± 2.39	4.71 ± 1.70	4.91 ± 1.77	NS
SD/Deep	81.3 ± 48.3	70.8 ± 44.0	69.56 ± 36.3	NS
Var %	9.96 ± 6.48	8.55 ± 5.84	8.39 ± 4.04	NS
Valsalva ratio	1.86 ± 0.5	1.99 ± 0.37	1.82 ± 0.38	NS
Tilt ratio	1.46 ± 0.27	1.45 ± 0.29	1.35 ± 0.15	NS

twins, and 9.9 among the referent twins, who had not been exposed to neurotoxic substances. Intrapair correlation was high among provocation tests (0.601, $P < 0.01$ for Valsalva ratio, 0.731, $P < 0.001$ for Tilt ratio), and no significant difference was seen between the exposure-discordant group and the nonexposed referents.

DISCUSSION

The present study did not detect any evidence of autonomic nervous system disturbances in twins exposed to organic solvents in their occupational surroundings, when compared with their twin pairs or other nonexposed referent twins. In the light of our previous observations some considerations are necessary.

The general exposure level of the subjects was rather low, as could be expected in a country with well organized occupational safety and health policies. All of the subjects were asymptomatic, and they had been chosen for the study because of their prereported exposure, which was ascertained. This largely excludes selection bias, which is always inherent in most studies dealing with symptomatic subjects. Our previous observations about disturbances of the cardiovascular reflexes among workers exposed to solvents do not contradict the present findings, since selection of symptomatic patients is obvious. In another study, we could also demonstrated slight changes of the cardiovascular function at a group level among heavy drinkers [10], as well as among diabetics with peripheral neuropathy [8]. Hence, our method is sensitive enough to show slight autonomic dysfunction in various states and it should have revealed disturbances also among the exposed twins, should there have been such abnormalities.

Another interesting aspect is that although interpair variation of the reflex parameters was demonstrated, only slight intrapair variation was observed, suggesting hereditary regulation of the cardiovascular reflexes. This further emphasizes the importance of co-twin control study model in any studies concerned with the nervous system effects of exogenous factors.

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