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REVIEWS

CASE REPORT

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ARTERIAL STIFFNESS IN CZECH POPULATION MEASURED BY VASERA® 1500

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ABSTRACT

The traditional non-invasive method for the early detection of arteriosclerosis is the brachial-ankle pulse wave velocity (PWV); however, this method is significantly influenced by blood pressure (BP) changes. Recently, a new non-invasive method for the arterial stiffness assessment was developed – the cardio-ankle vascular index (CAVI). This method has been shown to be unaffected by BP variations and thus it could be recommended for wide clinical use, including large population studies. The aim of this paper was to evaluate the CAVI in a sample of Czech adult population. A group of 121 healthy subjects (aged from 20 to >70 years) was examined using the newest type of non-invasive monitoring system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan). This control group was then compared with 3 groups of patients with selected lifestyle-related diseases: coronary artery disease (CAD; n = 74), diabetes mellitus (DM; n = 36), and hypertension (HT; n = 58). The statistical analysis showed a significant difference in the CAVI parameter between healthy subjects and patients with coronary artery disease, diabetes, and hypertension; the mean CAVI value in the control group (6.9) was significantly lower compared to the patients with CAD (CAVI = 9.2; $P < 0.001$ vs. control group), diabetes (CAVI = 8.5; $P < 0.001$ vs. control group), and hypertension (CAVI = 8.9; $P < 0.001$ vs. control group). These results demonstrate that CAVI should be considered as an important clinical parameter independent

of blood pressure changes, and should be recommended as a valuable indicator of the preventive evaluation of the arteriosclerotic risk in healthy subjects and patients with life-style related diseases.

INTRODUCTION

A World Health Organization (WHO) report estimates that around 20 million (32%) of total deaths result from various forms of life-related diseases (including CAD), many of which are preventable by action on the major primary risk factors. CAD and stroke are no longer only diseases of the developed world; some 70% of all CAD deaths worldwide took place in developing countries, while these countries also accounted for 80% of the global CAD disease burden. The above-mentioned WHO report estimates that CAD will be the leading cause of death in developing countries by 2010. Therefore, early detection of the arteriosclerotic plaque development is of crucial importance. Up to the present, the widely used method has been represented by evaluation of the brachial-ankle pulse wave velocity (PWV). However, several studies reported a significant dependence of PWV on blood pressure variations, so that the value of the measurement is seriously compromised [1]. Due to this limitation, a new and simple instrument for the early diagnosis of arteriosclerosis is of great interest. Recently, the device VaSera® was developed as a new non-invasive screening tool in the fight against atherosclerosis, which is a considerable cause of CAD. VaSera measures vascular compliance using a sophisticated new oscillometric technology termed CAVI or Cardio-Ankle Vascular Index, used for the quantitative assessment of arterial wall stiffness. According to some recent studies, the parameter CAVI is less influenced by blood pressure changes (2, 3). The aim of this study was to investigate: [1], the influence of blood pressure changes on CAVI in Czech healthy adult subjects; and [2], the differences in the value of CAVI between healthy subjects and patients with selected lifestyle-related diseases: coronary artery disease (CAD), diabetes mellitus (DM), and hypertension (HT) .

PATIENTS AND METHODS

Patient selection

A group of 121 healthy subjects (men and women) aged from 20 to >70 years was recruited in St. Anne's Faculty Hospital in Brno (Czech Republic) and examined using the newest type of non-invasive monitoring system VaSera® 1500 (Fukuda Denshi Co., Tokyo, Japan). This control group was then compared with 3 groups of patients with selected lifestyle-related diseases: coronary artery disease (CAD; n = 74), diabetes mellitus (DM; n = 36), and hypertension (HT; n = 58).

METHODS

Cardio-ankle brachial index (CAVI) – according to Yambe et al. [1]

CAVI reflects the stiffness of the artery from the heart to the ankles. As arteriosclerosis progresses, the CAVI value becomes higher. CAVI is calculated based on the stiffness parameter β, which is measured by carotid echography or the like, and is not affected by blood pressure. Thus, it represents natural vascular stiffness. The latest type of the VaSera device, VaSera 1500®, adopts the oscillometric method for blood pressure measurement. In addition, it does not simultaneously measure blood pressure at 4 limbs but at first it measures blood pressure at the right brachial and ankle and then it measures at the left brachial and ankle. Thus, arteries at the right and left sides are alternately pressurised with the other side open. This not only reduces burden to examinees but also enables more accurate measurement. CAVI calculation is based on the stiffness parameter β. This is an index to diagnose sclerotic degrees of the carotid artery, etc. from the diametrical variation and blood pressure measured by ultrasonic echography and represents the natural vascular stiffness independent of blood pressure. CAVI is calculated using the stiffness parameter β obtained by means of the Bramwell-Hill equation [4].

The stiffness parameter β

$$\beta = [\ln Ps/Pd] \cdot [D/\Delta D] \quad \cdots (1)$$

Ps : Systolic pressure
Pd : Diastolic pressure
D : Diameter
ΔD : Change of Diameter

From the Bramwell-Hill equation (here, the ratio of volumetric change, V/ΔV, is converted to the ratio of luminal change, D/ΔD)

$$PWV^2 = \frac{\Delta P}{2\rho} \cdot \frac{D}{\Delta D} \quad \cdots (2)$$

$$\frac{D}{\Delta D} = \frac{2\rho}{\Delta P} \cdot PWV^2 \quad \cdots (2)'$$

CAVI is obtained by substituting the equation [2]' for D/ΔD in equation [1].

The final equation of CAVI

$$CAVI = [InPs/Pd] \cdot \frac{2\rho}{\Delta P} \cdot PWV^2 \quad \cdots (3)$$

Ps : Systolic pressure Pd : Diastolic pressure
PWV : Pulase wave velocity between heart and ankle
ρ : Blood density ΔP : Pulse pressure

The reference values of CAVI are as follows:

CAVI < 8.0	normal range
8.0 =or< CAVI < 9.0	borderline
9.0 =or< CAVI	arteriosclerosis suspected

In order to limit as much as possible the influence of diurnal variations all the subjects were examined during a stable time period, between 7:00 AM and 10:00 AM. All the subjects were asked to avoid caffeine drinks in the morning. The examinations were conducted in a quiet room and at a stable temperature of 21–22 °C. The influence of blood pressure changes on CAVI was evaluated only in the control group (healthy subjects). The correlation between the R-CAVI and L-CAVI, as well as the correlations between CAVI and age, systolic and diastolic pressure were examined only in the control group.

STATISTICS

Visualisation of the data is based on comparative histograms and box-whisker plots. The descriptive summary of L (left) and R (right) values of CAVI is based on robust non-parametric statistics, i.e. median and 5th–95th percentile range. The statistical significance of the difference between L and R values was tested by a Wilcoxon paired test. The statistical significance of the differences in averaged values of CAVI among the different groups of examined subjects was evaluated using one-way ANOVA followed by a Tukey post-hoc test; the variables were described using the mean and its 95% confidence interval. The Pearson correlation coefficient was applied for the analysis of the relationship between CAVI and other descriptors (R and L side, age, systolic and diastolic blood pressures). The level of statistical significance was established at $P < 0.05$.

RESULTS

Statistical analysis showed that there is no significant difference between the right (R) and left (L) values of CAVI. The mean CAVI value in the control group (without signs of atherosclerotic diseases) was 6.9 ± 0.5. CAVI in patients with CAD was 9.2 ± 0.3 ($P < 0.001$ vs. control group) and in the group of diabetic subjects it was 8.5 ± 0.3 ($P < 0.001$ vs. control group). Finally, in the group of patients with hypertension the CAVI was 8.9 ± 0.3 ($P < 0.001$ vs. control group). These results suggest that the mean CAVI value is significantly higher in the patients with selected life-related diseases, and thus it reflects quantitatively the extent of the arteriosclerotic process. The results also revealed the presence of a strong correlation between R-CAVI and L-CAVI ($r = 0.963$; $P < 0.001$) and between the mean CAVI (R and L) and the age ($r = 0.756$; $P < 0.001$). A weak correlation was found out between the mean CAVI (R and L) and systolic blood pressure ($r = 0.355$; $P < 0.001$), and the mean CAVI (R and L) and diastolic blood pressure ($r=0.354$; $P < 0.001$). These results indicate that CAVI is not dependent on blood pressure variations.

DISCUSSION

The mortality caused by the so-called life-related diseases in the developed countries has become the highest in the world. It has been shown that these diseases are strongly associated with the lifestyle and inactivity, favouring plaque formation and atherosclerosis development. Social needs for quantitative measurement of atherosclerosis were rapidly increasing because the arteriosclerotic process is considered as an independent risk factor for cardiovascular diseases. The vessel wall arteriosclerotic changes represent the main risk for the onset of myocardial infarction and stroke; both complications vitally worsen the prognosis and the quality of life in the populations of developed countries (5, 6). For these reasons, a preventive and simple quantitative method for early diagnosis of arteriosclerosis is required.

The measurement of the aortic pulse wave velocity (PWV) is calculated by measuring the pulse transit time and the distance travelled between two selected sites (ie, arterial distance over transit time), which is inversely related to the distensibility of the arterial walls. PWV is still popularly practiced and its usefulness in the early diagnosis of arteriosclerosis was demonstrated (7, 8), but it had an inherent limitation of blood-pressure dependency [1]. Aortic PWV is pressure dependent, and PWV must be corrected for diastolic blood pressure [9] and carotid and femoral pulse waves are often difficult to detect, thus limiting the use in daily clinical practice. Hayashi et al. proposed the concept of an arterial stiffness β index [10]; however, stiffness β reflects only the regional (local) arterial stiffness, is expensive, and requires specialised ultrasonic equipment. Intima-media thickness (IMT), also called intimal medial thickness, was also becoming popular. IMT is a measurement of the thickness of artery walls, usually by external ultrasound, occasionally by internal, invasive

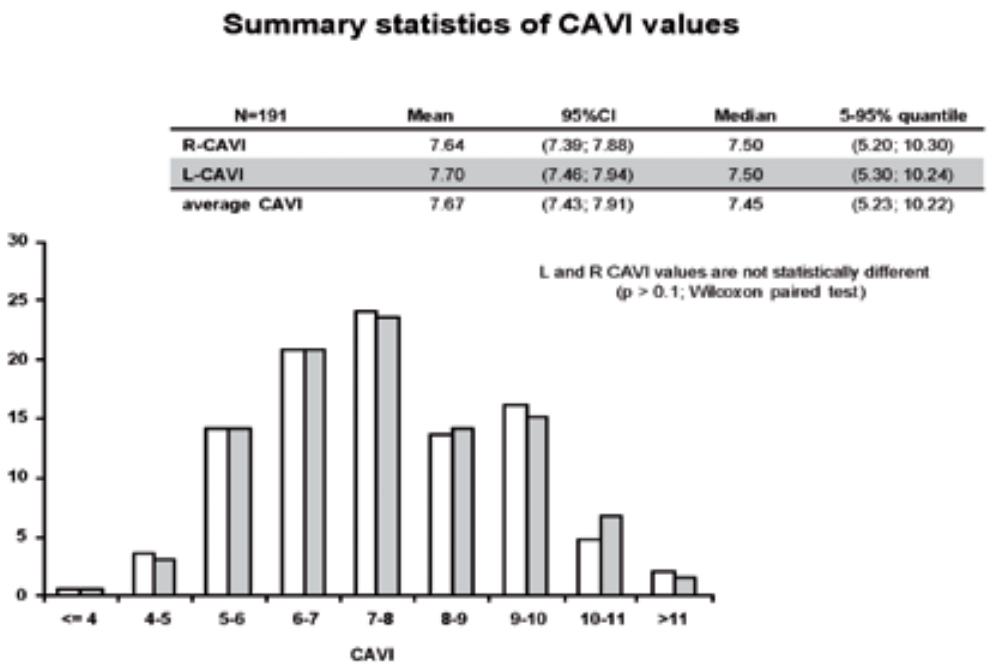

Figure 1
The summary statistics of the healthy subjects and the average CAVI (± SD) for each age group.

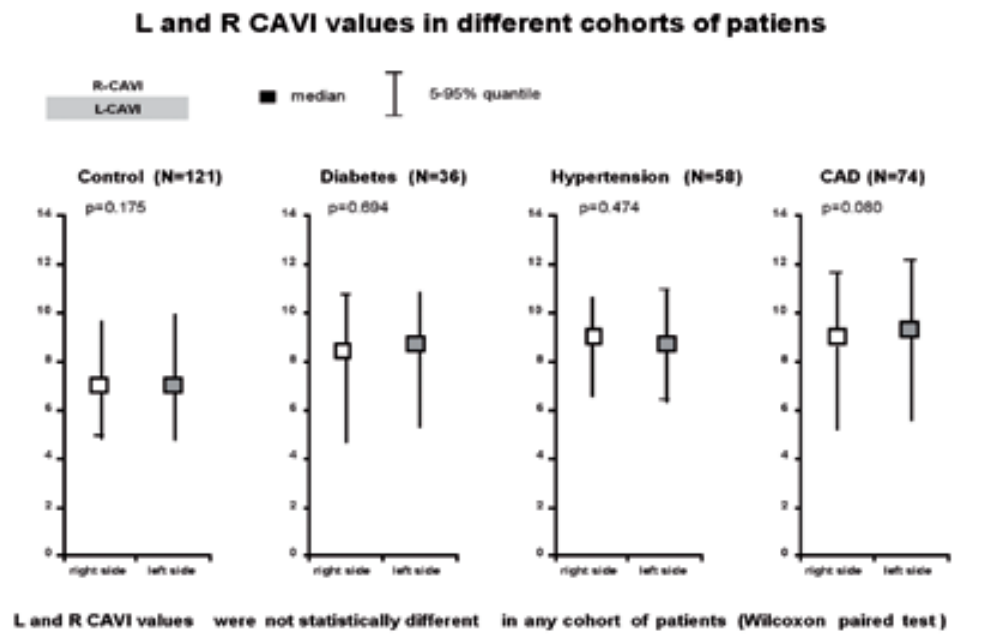

Figure 2
The results of the averaged R and L-CAVI values in the healthy subjects (controls) and in the groups of patients with diabetes, hypertension, and CAD.

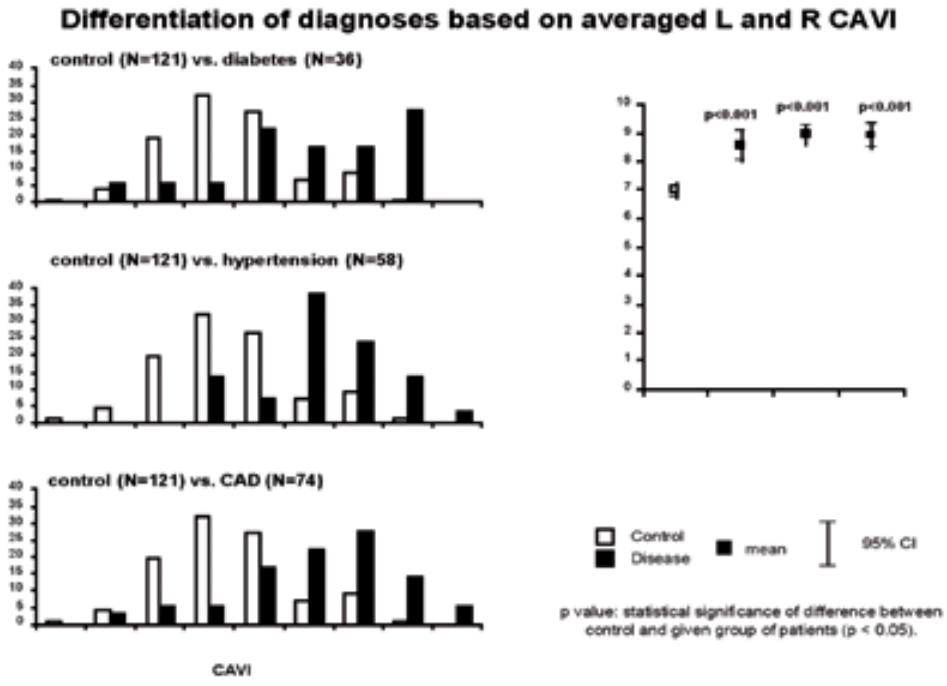

Figure 3
The significant differences of the averaged CAVI values in the control group and in the patients with diabetes, hypertension, and CAD.

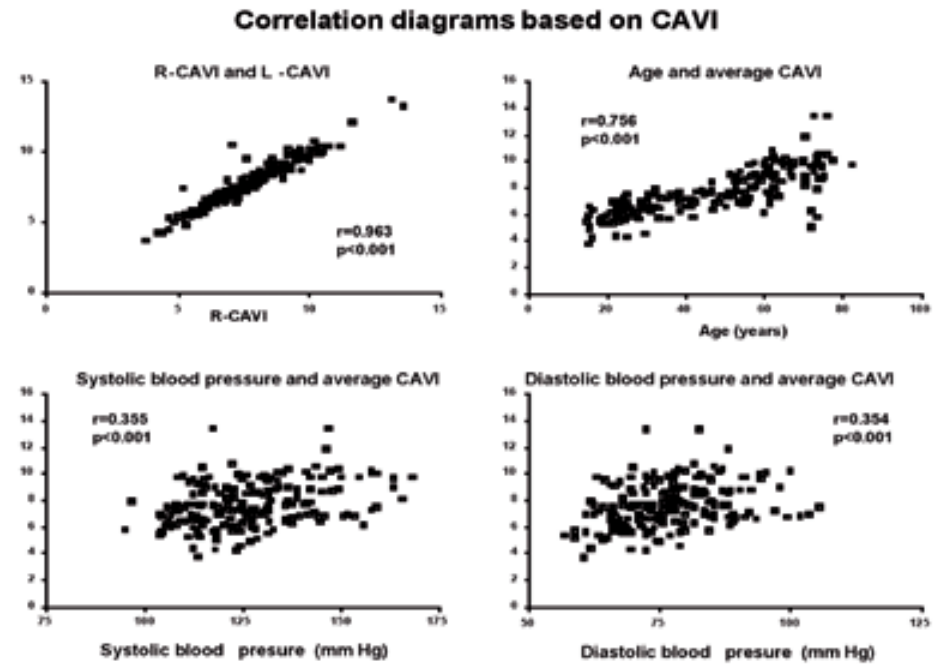

Figure 4
The correlation diagrams between the averaged values of L-CAVI and R-CAVI, between averaged CAVI and the age, and between averaged CAVI and systolic and diastolic BP.

ultrasound catheters, to both detect the presence and track the progression of atherosclerotic disease in humans [11]. IMT has been increasingly used in medical research since the mid 1990's and its key advantages are the lower cost (compared with most other methods), relative comfort for the patient, and lack of need for invasive methods or any X-ray radiation. IMT can be used repeatedly, over years, without compromising the patient's short- or long-term health status. However, IMT is limited to the morphological local regional measurement, and not to obtaining a representative image of the functional aspect in arterial stiffness. Radiographic IMT using advanced computed tomography (CAT) scanners is more approximated due to its ability to use software to more slowly and carefully process the images and the examination of the artery segments from whatever angle appears most appropriate [12] However, the major limitation of all CAT scanners is the dose of X-rays delivered to the patient's body, and there are also concerns about the safety of repeated doses of X-rays to track the disease status over time.

It has been known that lowered extensibility of the aorta causes onset of the heart disease and so determines the prognosis. Arteriosclerosis generally progresses from the aorta to both carotid arteries and then to the cerebral and coronary arteries [13]. For the accurate non-invasive evaluation of the stiffness of the aorta, femoral artery and tibial artery, the cardio-ankle vascular index (CAVI), which is independent of blood pressure, was developed. CAVI is a simple test, similar to PWV, but the main unique difference is that CAVI is not influenced by blood pressure fluctuations during the measurement and CAVI could be used as a reliable index of arterial stiffness even in subjects with labile blood pressure. Also, our results indicated that CAVI is not dependent on blood pressure variations, and this is an important finding opening the possibility to evaluate e.g. the proper effects of antihypertensive drugs on blood pressure and arterial stiffness [2]. The variation coefficient for CAVI is 3.8 %, and the reproducibility seems to be sufficient enough for clinical application [2]. The regions measured by both CAVI and PWV include elastic and muscular vessels (aorta and femoral–tibial arteries) and the calculation formula for CAVI is fully compatible with the aortic PWV measured by conventional methods. Coronary artery ischaemic disease, diabetes mellitus, and hypertension induce severe arteriosclerotic changes resulting in increased arterial stiffness, and represent a major risk factor of arteriosclerosis development [14]. The significant difference in the mean CAVI values between healthy subjects and the patients with the three above-mentioned life-related diseases in this study seems to support this fundamental idea. It is also well known that arteriosclerosis increases with age [15], and our results showed that CAVI increases with age too, and thus age should be regarded as a strong risk factor. In other words, the higher value of CAVI reflects the extent of the plaque formation, and this further highlights the predictive value of CAVI for arteriosclerotic risk [16].

CONCLUSION

In conclusion, CAVI assessed by the device VaSera® 1500 is a simple and valuable clinical test for the estimation of arterial stiffness. CAVI is not influenced by blood pressure variations, and is therefore very useful for the early detection of plaque formation in healthy subjects and for monitoring the arteriosclerosis progression in patients with life-related diseases. However, the number of subjects included in this study was not sufficient (121 healthy volunteers only) and further large population studies are needed.

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CARDIOVASCULAR REHABILITATION PROGRAMME IN MEN AFTER ACUTE MYOCARDIAL INFARCTION

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INTRODUCTION

Cardiovascular exercise training is very important in the complex care of patients with cardiovascular disease. It starts already during hospitalisation and after the discharge to home care it continues in the form of a controlled outpatient rehabilitation programme of individual training at home [1]. It increases physical fitness, improves the quality of life (2–4), and decreases cardiovascular mortality (5,6). Dynamic endurance aerobic activities are the basis of each training unit (7–9,13,14). The best-known and most widespread type of aerobic training is training with continuous workload. Interval training (1,10) can be an alternative training method for persons with a low tolerance of load, with a lower contractility of left ventricle, or for elderly people.

AIM OF THE STUDY

The aim of the present study was to evaluate the effect of a 12-week controlled outpatient rehabilitation programme with continuous and interval workload on aerobic capacity and performance on the level of anaerobic threshold in men after acute myocardial infarction (AMI) treated by percutaneous thoracoplasty of the coronary artery (PTCI with stent implantation).

SET OF PATIENTS

Forty-four male patients after AMI were included into the study. They were divided into two groups. The first group with ejection fraction (EF) 52 ±7 %, group K, n=22, went in the aerobic phase through the training with continuous workload, the second group with EF 49 ±12 %, group I, n=22, went in the aerobic phase with the interval training.
Controlled outpatient rehabilitation was started within 12 weeks after AMI. AMI diagnosis was identified at 1st Dept. of

Internal Medicine/Cardioangiology of the Faculty of Medicine, Masaryk University, St. Anne's Faculty Hospital in Brno (treated by PTCI with stent implantation). During the rehabilitation all patients were symptomatically stable and their medication was not changed.

The groups did not differ in age and ejection fraction; their characteristics are given in Table 1.

Table 1
Characteristics of the patient set

	Group K	Group I
Number (n)	22	22
Age (years)	57 ± 12	60 ± 7
Ejection fraction (%)	52 ± 7	49 ± 12
Starting RHB (weeks after AMI)	6 ± 2.5	5 ± 3.4

METHODOLOGY

Methods of examination

Before the beginning of the rehabilitation (RHB) programme and after its completion we made a spiroergometric examination to the symptom-limited maximum (Pulmonary Function System 1070, MedGraphics, USA). The examination was started by monitoring resting EKG in lying and sitting position (Schiller CS 100), followed by 3-minute adaptation in sitting position on an ergometer. The workload was increased every 2 minutes by 20 W to the symptom-limited maximum. Anaerobic threshold was determined from the course of changes of ventilatory-respiratory parameters. For the use of RHB it was expressed in watts, heart rate, and degrees of RPE (Borg scale).

Before the beginning of resistance training (i.e. in the 3rd week of the RHB programme) we made an isometric test ("handgrip", DHG-SY3, Recens) to verify blood pressure response to isometric load. In the case of a normal response the entrance 1-RM test (one repetition maximum test) was made in three exercises of resistance training. The test was repeated in the 6th week and in the 12th week of the RHB programme.

Rehabilitation programme

The controlled outpatient RHB programme lasted 12 weeks altogether with a frequency of three times a week. The training unit lasted for 60 minutes and consisted of a warm-up phase (10 min), an aerobic phase (1st to 2nd week, 40 min; 3rd to 12th week, 25 min), a toning phase (3rd to 12th week, 15 min) and a relaxation phase (10 min). The patients in the "K" group went in the aerobic phase through continuous training, in "I" group they went through interval training. For the interval training the following modification was chosen: 30 s of working phase with the intensity on the level of anaerobic threshold, and 60 s of relaxation phase with a minimum workload of 5 watts.

The interval training was indicated by residual ischaemia, low ejection fraction of left ventricle, and generally low tolerance of workload.

The warm-up phase was aimed at preparing the cardiovascular and motor systems for further load, prevention of musculoskeletal lesion. The warm-up phase was composed of dynamic endurance exercises (simple floor gymnastic exercises, exercises with gymnastic apparatus) and stretching of muscle groups with a tendency to shortening.

The aerobic phase was effected on a bicycle ergometer (Ergoline REHA E900) controlled by the ErgoSoft+ for Windows program. The aerobic training intensity was determined on the anaerobic threshold level.

The resistance training was realised on TK-HC COMPACT multifunctional muscle conditioning machines. Four exercises were done (bench press, pulldown, leg extension on the machine and sitting-lying positions). The resistance training intensity was determined by the 1-RM method and training loads were determined in per cent of maximum: 30–60 % 1-RM, weekly increase by 10 %). The number of sequences was 3 to 5 with ten repetitions. Before starting the resistance training, the patients were thoroughly informed about proper breathing and the technique of doing exercises.

Modified Schultz autogenic training was used for relaxation.

In the course of the whole training, monitoring of heart rate, blood pressure and degree of RPE was done; during the aerobic phase EKG was also carried out.

Statistical processing

Statistical processing was made in the Microsoft Excel and Statistica, version 8 programs. Distribution was tested by Lillefors modification of the Kolmogorov-Smirnov test of normality. According to the result either a paired *t*-test or the Wilcoxon test for dependent specimens were used. The significance level was determined at 0.05; at this level of statistical significance the testing was made on the level 0.01 (0.001). The results are presented as means with standard deviations.

RESULTS

After the completion of the programme a statistically significant increase of oxygen intake on the level of anaerobic threshold was recorded in both groups (Table 2). In the "K" group VO_2ANP increased by 13 %, VO_2ANP/kg by 11 %. In the "I" group VO_2ANP increased by 20 %, VO_2ANP/kg also by 20 %. The tolerance of workload on the level of anaerobic threshold also improved statistically significantly in both groups (Table 3). In the "K" group WANP increased by 15 % and

Table 2
Parameters of aerobic capacity on the level of anaerobic threshold

	Group K		p	Group I		p
	Before RHB	After RHB		Before RHB	After RHB	
VO_2ANP ($ml.min^{-1}$)	1086±190	1225±291	0.001	995±209	1194±242	0.05
VO_2ANP/kg ($ml.min^{-1}.kg^{-1}$)	12.9 ± 1.7	14.3 ± 2.5	0.01	11.6 ± 3.30	13.9 ± 3.71	0.05

VO_2ANP = oxygen intake on the level of anaerobic threshold

Table 3
Performance parameters on the level of anaerobic threshold

	Group K		P	Group I		p
	Before RHB	After RHB		Before RHB	After RHB	
WANP (W)	62 ± 14.2	71 ± 19.4	0.01	52 ± 10.2	70 ± 16.1	0.001
WANP/kg ($W.kg^{-1}$)	0.7 ± 0.17	0.8 ± 0.19	0.01	0.6±0.17	0.8 ± 0.26	0.001

WANP = performance on the level of anaerobic threshold

WANP/kg by 17 %. In the "I" group WANP increased by 35 % and WANP/kg by 37 %.

DISCUSSION

The training with continuous workload and the interval training have been widely used not only in sports activities, but also in rehabilitation. The interval training in cardiovascular rehabilitation is often recommended and conducted individually with regard to the health and functional state, to the age and gender of the patient. Workload intensity, duration of working and relaxation phases in interval training, and the total number of exercise intervals differ according to the orientation of the training (10–12). Mífková et al. [11] used in her study the following modification of interval training: 30 s of working phase on the level of anaerobic threshold and 60 s of relaxation phase on the level of 5 watts. Altogether, 38 men with ischaemic heart disease were monitored in the study. Both groups differed in age and ejection fraction. The total work done by the patients in this interval training modification was 2.5 to 3 times lower than in the group of patients for whom continuous training had been prescribed. In the final spiroergometric examination there was no statistically significant difference between the groups with interval and continuous training either in performance parameters or in parameters of aerobic capacity (evaluated on the level of the highest values achieved). Both in the interval and continuous types of the training similar results were obtained at the same training workload intensity.

In our study the same modification of interval training was used: 30 s of working phase with intensity on the level of anaerobic threshold and 60 s on the level of 5 W). We evaluated selected parameters on the level of anaerobic threshold. The patients in our group did not differ in age and in ejection fraction. The benefit of interval training lies in the possibility of obtaining improvement even in risk patients [11].

CONCLUSION

The group with interval training (I) had already before the starting of the programme a lower oxygen intake and a lower tolerance of workload than had the group with continuous training (K). After the completion of the programme the oxygen intake on the level of anaerobic threshold increased statistically significantly in both groups (in the "K" group VO_2ANP increased by 13 %, VO_2ANP/kg by 11 %; in the "I" group VO_2ANP increased by 20 %, VO_2ANP/kg also by 20 %). The tolerance of the workload increased statistically significantly on the level of anaerobic threshold in both groups. (In the "K" group WANP increased by 15 % and WANP/kg by 17 %; in the "I" group WANP increased by 35 % and WANP/kg by 37 %.) A statistically significant improvement of the monitored parameters after the 12-week rehabilitation programme was recorded in both groups. Both types of the training were well tolerated.

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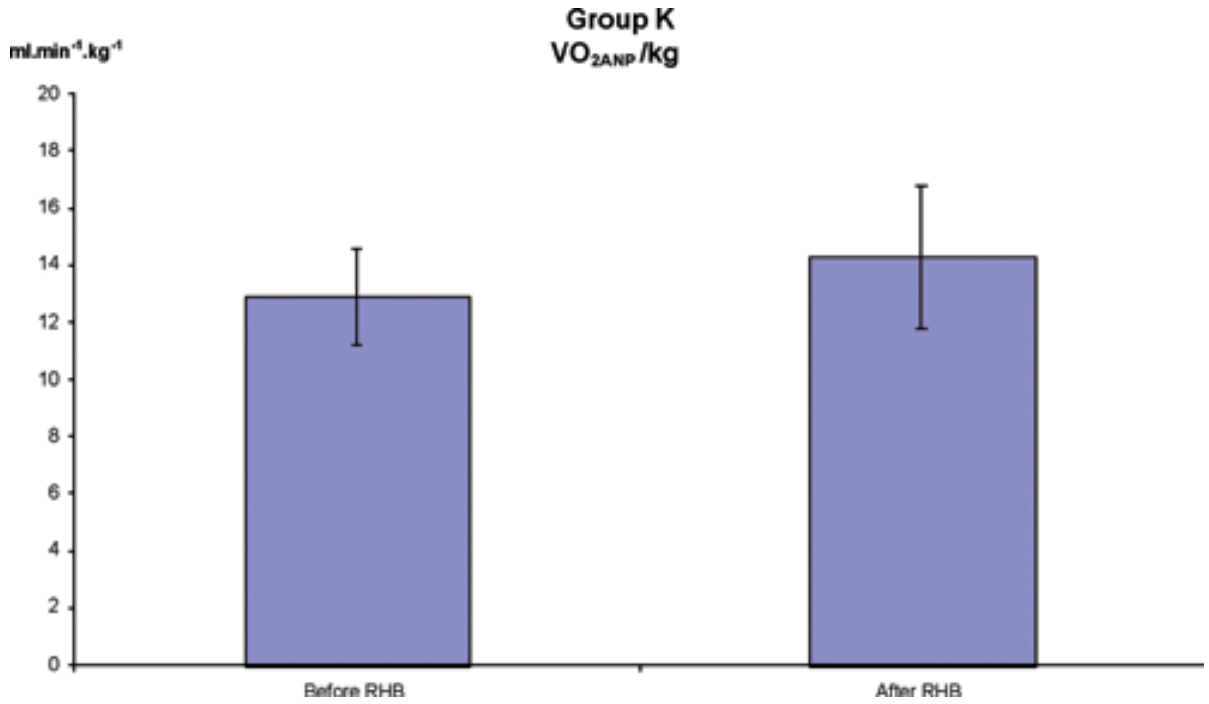

Figure 1
Oxygen consumption before and after cardiovascular exercise training at the level of anaerobic threshold in group K ($p < 0.01$)

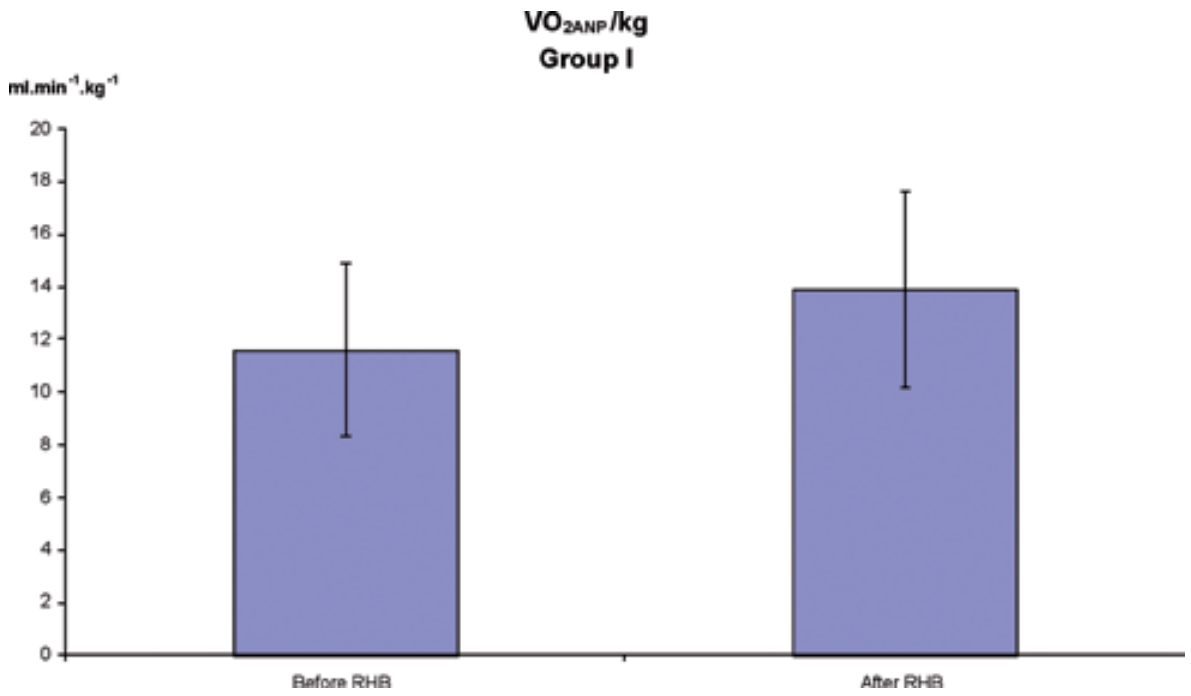

Figure 2
Oxygen consumption before and after cardiovascular exercise training at the level of anaerobic threshold in group I ($p < 0.01$)

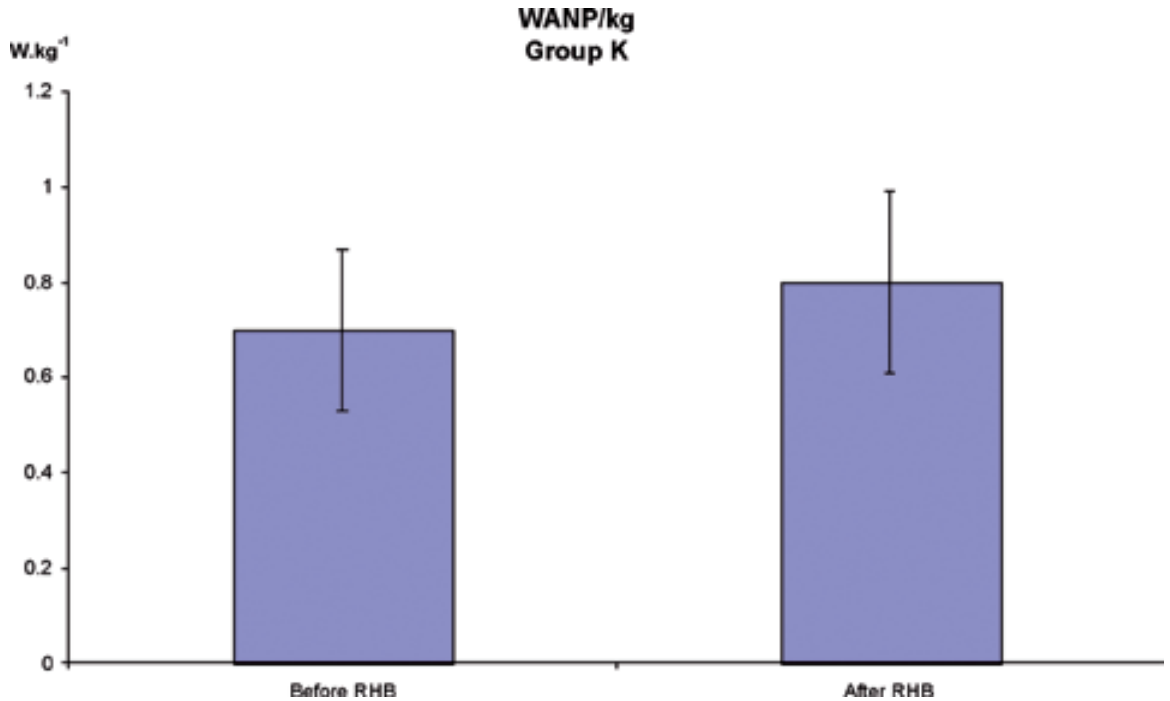

Figure 3
Workload before and after cardiovascular exercise training at the level of anaerobic threshold in group K ($p < 0.01$)

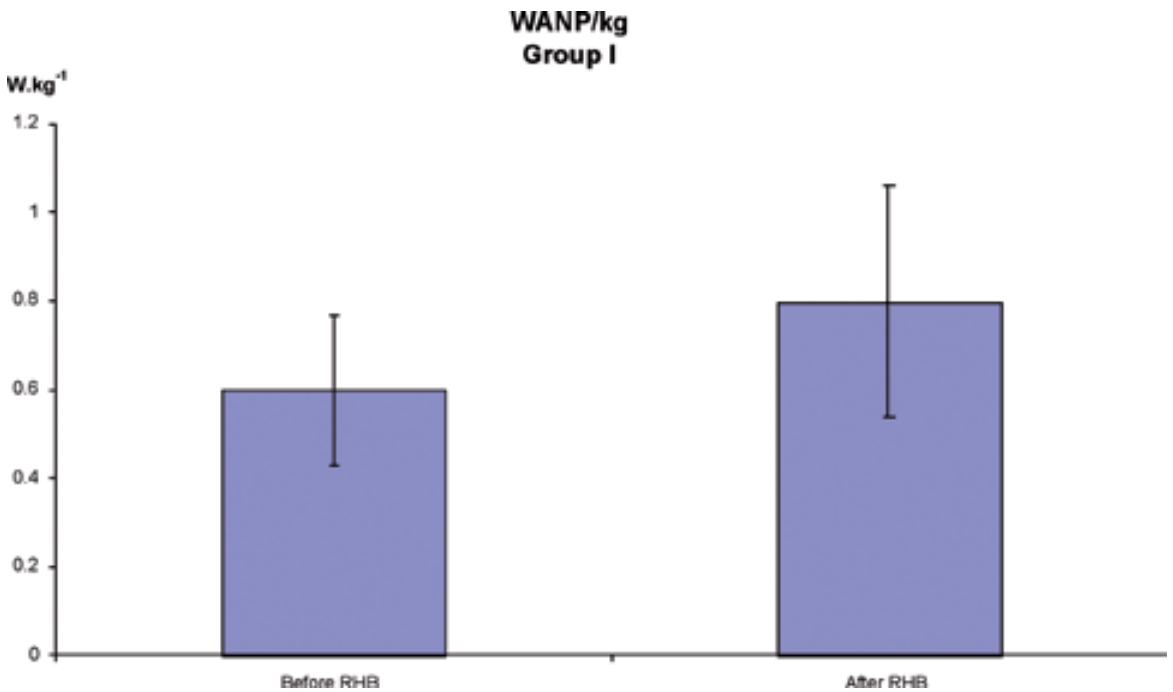

Figure 4
Workload before and after cardiovascular exercise training at the level of anaerobic threshold in group I ($p < 0.01$)

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COMBINATION OF AEROBIC AND RESISTANT TRAINING IN MULTIPLE SCLEROSIS

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ABSTRACT

The aim of this study was to analyse the effect of an 8-week rehabilitation programme consisting of the aerobic and resistant training forms on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue, and functional independence in a group of patients with Multiple Sclerosis (MS).

At the beginning and at the end of the study we examined 15 MS patients with a clinically active form of MS (age 50.7 ± 13.1 years, 12 women, 3 men, mean duration of MS 15.4 ± 14.4 years, EDSS 2.8 ± 0.7), who participated in the rehabilitation programme. The diagnosis was made at the 1st Dept. of Neurology. The patients underwent a clinical examination, MS activity rating (EDSS), symptom-limited bicycle spiroergometry (MedGraphics), spectral analysis of heart rate variability by a Task Force Monitor (frequency band LF, HF, TP, and sympathovagal balance LF/HF), and an extremity muscle strength evaluation (1-RM). The patients were also tested for fatigue (MFIS questionnaire) and functional independence (FIM).

The outpatient RHB programme controlled was designed for 8 weeks with a frequency of twice a week. The training unit lasted for 60 to 90 minutes and consisted of a warm-up phase (10 min), an aerobic phase (1st to 2nd week 20–40 min; 3rd to 8th week 25 min), and a relaxation phase (10 min). Resistant training was added to the training unit in the 3rd week of the RHB programme (3rd to 8th week 15–20 min). ECG, blood pressure, and RPE were monitored during the aerobic phase for safety reasons. Three exercises were performed: bench press, pulldown, and leg extension. The intensity of resistant training was determined by the 1-RM method. The patients started resistance exercises at 30–60% 1-RM with a weekly increase of 10%. All three exercises were repeated 10 times in 3 to 5 sets.

A comparison of the entrance and final values showed a significant improvement of functional capacity, namely in the values of spiroergometry parameters ($P<0.05$, Wilcoxon paired test) W_{SL} (94.4 ± 25.0 vs. 102.7 ± 27.9 W, $p = 0.042$), $W_{SL}.kg^{-1}$ (1.4 ± 0.3 vs.1.5 ± 0.4 $W.kg^{-1}$, $p = 0.026$), VO_{2SL} (1463.1 ±

Table 1
Basic anthropometric data and MS disease activity description of the group of MS patients examined (mean ± SD)

Women / men	12 / 3
Age (years)	50.7 ± 13.1
Height (m)	1.7 ± 0.1
Weight (kg)	69.1 ± 8.9
Body mass index (BMI)	24.9 ± 3.3
Clinical disability (EDSS)	2.8 ± 0.7
MS duration (years)	15.7 ± 14.4
Primary progressive form of MS (n)	1 (6.7 %)
Secondary progressive form of MS (n)	5 (33.3 %)
Relapsing remitting form of MS (n)	9 (60.0 %)
Unaided walking (n)	11 (73.3 %)
Walking with 1 or 2 crutches (n)	4 (26.7 %)
Spastic paraparesis (Ashwoth ≤ 2; n)	2 (13.3 %)
Without MS-specific pharmacotherapy (n)	6 (40.0 %)
Immunomodulants (Interferon, Betaferon, Copaxon, Rebif; n)	7 (46.7 %)
Corticotherapy (Medrol, Solumedrol, Imuran, Prednisone; n)	2 (13.3 %)

359.2 vs. 1578.4 ± 390.3 mlO_2, p = 0.015), and also in the values of muscle strength in bench press (22.3 ± 9.3 vs. 28.1 ± 9.7 kg, p = 0.0001), pulldown (22.1 ± 11.3 vs. 28.3 ± 11.3 kg, p = 0.0001), and leg extension (26.5 ± 8.3 vs. 30.9 ± 9.0 kg, p = 0.001). We detected a positive significant impact of the rehabilitation programme on the MFIS self-perception fatigue scale (28.5 ± 17.6 vs. 26.0 ± 14.9, p = 0.018; MFISp 14.6 ± 8.3 vs. 13.3 ± 6.9, p = 0.043). The other parameters under study did not achieve statistical relevance. We consider the increase in HRV spectral powers as a sign of improving adaptability of autonomic cardiovascular regulation. The clinical status (EDSS) and functional independence (FIM) were not influenced by the exercise training load and the length of the rehabilitation programme.

We can conclude that the results of our study demonstrate a possibility of influencing some of the physical fitness parameters, muscle strength, and self-perceived fatigue after 8 weeks of the rehabilitation programme realised twice a week with a combination of the aerobic and resistant training forms in a group of MS patients with mild to moderate clinical disability (EDSS 2.8 ± 0.7).

INTRODUCTION

Multiple sclerosis (MS) is a chronic systemic autoimmune disease that causes functional neurological deficit on the basis of dissemination of demyelinisation focuses in the central nervous system (CNS) area [1]. The probable cause of the persisting neurological deficit is the axon involvement which appears at the beginning of the disease. The maximum axon loss occurs in the first years of the disease (the period with minimal disability and clinical finding). As a result of depletion of the functional reserves of CNS, substantial deceleration in the conduction of nerve impulses develops. Further axon loss brings on an irreversible disability [2]. Demyelinisation and axon involvement are localised particularly in the periventricular area, brainstem, cerebellum, and lateral and posterior cords of the spinal chord. Predominant manifestations therefore include central pyramidal symptoms, cerebral, stem and sensitive symptoms, disorders of autonomic regulation, urinary incontinence, etc. [3]. Through demyelinisation processes, MS also attacks basic physiological response to work load. Functional changes in skeletal muscles, particularly reduction of the number of fibres of type I, reduction of oxidative abilities, and prevailing anaerobic activity of skeletal extrafusal fibres, are ranked among other pathophysiological processes [4]. Increasing disability leads to secondary signs – loss of physical condition with a gradual reduction of muscular mass, reduction of cardiorespiratory fitness including autonomic nervous system dysfunction and, finally, loss of functional independence (5, 6, 8, 9). Controlled exercise activity represents a significant element with impact on physical condition and course of MS disease.

PURPOSE

The aim of this study was to analyse the effect of an 8-week rehabilitation programme consisting of aerobic and resistant training forms on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue, and functional independence in a group of patients with Multiple Sclerosis (MS).

Table 2
Results of evaluated scales and questionnaires of the group of patients (mean ± SD)

Scale	Value	Min. – max. value
Clinical disability (EDSS)	2.8 ± 0.7	0–10
Fatigue (MFIS)	28.5 ± 17.6	0–84
MFISp – physical	14. ± 8.3	0–36
MFISc – cognitive	11.7 ± 8.6	0–40
MFISps – psychosocial	2.3 ± 1.9	0–8
Independence (FIM)	118.5 ± 10.4	18–126

Table 3
A comparison of anthropometric values, functional independence, and self-perceived fatigue before and after training programme (mean ± SD)

Parameter	Before training	After training	P
Weight (kg)	69.1 ± 8.9	68.2 ± 8.6	NS
Body mass index (BMI)	24.9 ± 3.3	24.5 ± 3.2	NS
Clinical disability (EDSS)	2.8 ± 0.7	2.7 ± 0.7	NS
Fatigue (MFIS)	28.5 ± 17.6	26.0 ± 14.9	* 0.018
MFISp – physical	14.6 ± 8.3	13.3 ± 6.9	* 0.043
MFISc – cognitive	11.7 ± 8.6	10.8 ± 7.4	NS
MFISps – psychosocial	2.3 ± 1.9	2.1 ± 1.6	NS
Independence (FIM)	118.5 ± 10.4	119.2 ± 8.4	NS

* $P < 0.05$, NS – without statistical relevance

METHODOLOGY

Forty patients with verified MS disease, members of the "Unie ROSKA Brno", treated at the 1st Department of Neurology, St. Anne's Faculty Hospital in Brno, were recruited for the study. Twenty of them fulfilled the entrance criteria for the study: the ability of the patient to undergo entrance and final examinations, aerobic training on a bicycle ergometer, and resistant training on multifunctional strengthening machines. The patients with internal, metabolic and other diseases with possible influence on the validity of the exercise test were excluded. A clinically unstable state of the disease, active autonomic nervous system (ANS) dysfunction, and medication affecting the cardiorespiratory system or ANS were also criteria of exclusion.

The study was approved by the Masaryk University Ethical Committee and all the MS patients who participated in the study confirmed the "Informed consent of the patient".

Twenty patients were included in the group of patients examined. Two of them were unable to finish the complete programme, 3 of them were excluded because of arrhythmias. The final group of patients consisted of 15 patients (12 women, 3 men). The general characteristics of the group of MS patients with the evaluation of disease activity (Kurtzke's Expanded Disability Status Scale; EDSS) are given in the table (Table 1 and Table 3).

The effect of the 8-week rehabilitation programme on the parameters of functional fitness, muscle strength, cardiovascular autonomic functions, fatigue, and functional independence in the group of patients with MS was evaluated by comparison of the results of the entrance examination before starting the rehabilitation programme and the final examination after completion of the programme.

The entrance and final examinations consisted of:

Kurtzke's Expanded Disability Status Scale (EDSS) – a standard scale for the evaluation of clinical disability in patients with MS [10]. It is a neurological examination that evaluates the impact of MS on 8 basic functional systems. The scale is divided into 20 levels in the interval from 0 (no functional disorder or impairment) to 10 (death due to MS).

Table 4
A comparison of cardiorespiratory values before and after training programme (mean ± SD)

Parameter	Before training	After training	P
W_{SL} (W)	94.4 ± 25.0	102.7 ± 27.9	* 0.042
W_{SL}. kg^{-1} (Watt. kg^{-1})	1.4 ± 0.3	1.5 ± 0.4	* 0.026
W_{ANP} (Watt)	53.5 ± 14.0	57.2 ± 13.6	NS
W_{ANP}. kg^{-1} (Watt.kg^{-1})	0.8 ± 0.2	0.8 ± 0.2	NS
VO_{2SL} (ml O_2)	1463.1 ± 359.2	1578.4 ± 390.3	* 0.015
VO_{2SL} . kg^{-1} (ml O_2.kg^{-1})	21.1 ± 4.4	22.8 ± 4.9	NS
VO_{2SL} . SF^{-1} (ml O_2.tep^{-1})	10.7 ± 3.0	11.2 ± 2.5	NS
MET_{SL}	6.0 ± 1.3	6.5 ± 1.4	NS

* P < 0.05, NS – without statistical relevance

Table 5
1-RM test values before and after training programme (mean ± SD)

1-RM test	Before training	After training	P
Bench press (kg)	22.3 ± 9.3	28.1 ± 9.7	*** 0.0001
Pulldown (kg)	22.1 ± 11.3	28.3 ± 11.3	*** 0.0001
Leg extension (kg)	26.5 ± 8.3	30.9 ± 9.0	*** 0.001

*** P < 0.001

Table 6
HRV results (logarithmically transformed, mean ± SD)

HRV parameter (controlled breathing 0.33Hz)	Before training	After training	P
Log LF	1.98 ± 0.44	2.07 ± 0.40	NS
Log HF	2.04 ± 0.46	2.03 ± 0.51	NS
Log TP	2.39 ± 0.36	2.45 ± 0.39	NS

LF – low-frequency band, HF – high-frequency band, TP – total power, NS – without statistical relevance

The Functional Independence Measure (FIM) – a scale for the evaluation of independence in basic daily activities [11]. Locomotor skills, mental functions, and the general degree of independence are evaluated within a range from 18 (full dependence) up to 126 (full independence) points.
The Modified Fatigue Impact Scale (MFIS; 12) is a questionnaire (21 items) expressing subjective assessment of fatigue impact on physical condition (MFISp), cognitive functions (MFISc), and psychosocial functions (MFISps). Answers to individual items can score from 0 (no fatigue present) to 4 points (almost permanent fatigue). The results of the evaluated scales and questionnaires of the group of MS patients examined are given in the table below (Table 2).

Symptom-limited spiroergometry was carried out in standard conditions [13] on a bicycle ergometer. The twelve-lead electrocardiogram was recorded (Cardiovit CS 100 – Schiller). Ventilation-respiration values were determined by a gas analyser (Pulmonary Function System 1070 – MedGraphics CPX/D, USA). The workload during the exercise test was increased every 2 minutes by 20 W up to the symptom-limited maximum. The anaerobic threshold was determined from the course of changes of ventilatory-respiratory parameters. For the use of rehabilitation it was expressed in watts, heart rate, and degrees of RPE (Borg's Rate of Perceived Exertion).
Heart rate variability (HRV) was examined by TASK FORCE MONITOR (CNSystem, Graz, Austria; 14). The examination was

carried out by means of non-invasive continuous recording of heart rate and beat-by-beat measurement of blood pressure. Five-minute recording was made at rest in supine position with metronome-controlled breathing (f = 0.33 Hz). The data were processed using spectral analysis in the low-frequency component of HRV (0.05–0.15 Hz; LF; [ms^2]), high-frequency component of HRV (0.15–0.50 Hz; HF; [ms^2]), total spectral power (TP; [ms^2]), and the index of sympathovagal balance (LF/HF). The examination was carried out in standard conditions (exclusion of physical activity 24 hours before examination, more than 4 hours after last meal, 8 hours without smoking and coffee or alcohol drinking, examination between 9 and 12 a.m.).

The controlled outpatient RHB programme was designed for 8 weeks at a frequency of twice a week. The training unit lasted for 60 to 90 minutes and consisted of a warm-up phase (10 min), an aerobic phase (1st to 2nd week 20–40 min; 3rd to 8th week 25 min), and a relaxation phase (10 min). Resistant training was added to the training unit in the 3rd week of the RHB programme (3rd to 8th week 15–20 min). ECG, blood pressure, and RPE were monitored during the aerobic phase for safety reasons.

The warm-up phase was aimed at preparing the cardiovascular and locomotor systems for further workload, prevention of musculoskeletal lesions. It consisted of dynamic endurance exercises, basic gymnastic exercises, and stretching of muscle groups with a tendency to shortening.

The aerobic phase was realised on a bicycle ergometer (Ergoline REHA E900) controlled by the ErgoSoft+ for Windows program. Interval or continuous workload training used for the aerobic phase was chosen according to the entrance spiroergometry examination (interval training was used in cases of generally low tolerance of workload intensity). The intensity of the training was set at the anaerobic threshold level. The interval training consisted of 30 s of working phase with the intensity at the level of anaerobic threshold and 60 s with a minimum workload of 5 watts.

The resistant training was added after the isometric exercise test ("handgrip", DHG-SY3, Recens) to verify physiological blood pressure response to isometric workload. In cases of normal response, the entrance one-repetition maximum test (1-RM test; [kg]**)** was made for three exercises of resistant training (bench press, pulldown, leg extension). The resistant training was provided on multifunctional strengthening machines (TK-HC COMPACT). Three exercises were performed: bench press, pulldown, leg extension. The intensity of the resistant training was determined by the 1-RM method. The patients started resistance exercises at 30–60 % 1-RM with a weekly increase of 10 %. All three exercises were repeated 10 times in 3 to 5 sets. Proper breathing and the technique of exercises were checked by a physiotherapist.

Modified autogenic training was used for relaxation at the end of the training unit.

Statistical processing was made using the Statistica software (STATISTICA, StatSoft, Inc. 2008, v. 8.0). Normality of distribution was tested by the Lilliefors modification of the Kolmogorov-Smirnov test. The Wilcoxon test for dependent samples was used to compare the entrance and final examination results. The results are presented as means ± standard deviations (SD).

RESULTS

A comparison of the mean anthropometric values, clinical disability, functional independence, and self-perceived fatigue before and after the training programme completion is given in the table (Table 4). Significantly lower values of MFIS and MFISp are demonstrated.

A comparison of the mean values of cardiorespiratory tolerance before and after the training programme completion is given in the table (Table 4). Significantly higher values of maximal symptom-limited workload and oxygen consumption are demonstrated.

A comparison of the mean values of 1-RM before and after the training programme completion is given in the table below (Table 5). Significant improvement in all of the exercises is demonstrated.

The HRV values evaluated were logarithmically transformed for the purposes of data distribution. A comparison of the mean values before and after the programme completion is given in the table below (Table 6).

DISCUSSION

The obtained results of our study concern a sample of MS patients with mild to moderate [16] clinical disability (2.8 ± 0.7, interval 1 to 4) and with a majority of the relapsing remitting form of the disease (9 patients, 60 %). The rehabilitation programme influenced neither the clinical status nor the functional independence measure. These findings could be caused by various factors. Only 20 % of the patients had major motor dysfunctions. The majority of disability causes were sphincter, sensitive, visual, and cerebellar dysfunctions. These dysfunctions could not be effectively improved by our programme. The results of our training programme could also be influenced by the insufficient length of the programme. The high level of functional independence in the group of MS patients tested at the beginning of the programme approximates the maximal FIM test values (118.5 ± 10.4; max. 126 points). We suppose the decrease from the maximal values to be caused mainly by sphincter, sensitive, visual, and cerebellar dysfunctions. These dysfunctions could be influenced by exercise training in a minimal extent only (118.5 ± 10.4 FIM

entrance examination values vs. 119.2 ± 8.4 FIM final examination values; 17, 18).

A very important finding was represented by a significant decrease in the MFIS self-perceived fatigue questionnaire (28.5 ± 17.6 vs. 26.0 ± 14.9, * 0.018) and its subscale evaluating physical impact of fatigue on health condition MFISp (14.6 ± 8.3 vs. 13.3 ± 6.9, * 0.043). On the basis of the results presented we consider that fatigue could be primarily influenced by physical training as described in the recent literature (19, 20, 21). Up to now, there are no relevant and consistent results available concerning the combined rehabilitation programme for MS patients [22].

Physical fitness and cardiorespiratory tolerance

The comparison of mean values of cardiorespiratory tolerance before and after the training programme demonstrated 8.7 % improvement in symptom-limited maximum workload and 7.8 % improvement in symptom-limited oxygen consumption. Our former pilot studies (23, 24, 25) demonstrated only a 4% improvement of $VO_{2SL}.kg^{-1}$ (6 MS patients, EDSS 4.3 ± 1). Other parameters were not statistically significantly influenced. It is surprising that Bjarnadottir et al. [26] demonstrated in a group of 16 MS patients (EDSS ≤ 4) a 14.7% improvement of peak oxygen consumption, an 18.2% improvement of peak workload, and a 27.3% improvement of peak workload on the anaerobic threshold level. The training programme (60 min) was designed for 5 weeks (3 times per week). It consisted of a warm up phase (3min, 33 % VO_{2max}), an aerobic phase on a bicycle ergometer (15–20 min, 55–70 % VO_{2max}), a resistant phase with 13 exercises (upper and lower extremities, trunk muscles, 15 to 20 repetitions), and 5 minutes of stretching with relaxation. The evident difference in the physical fitness results could be probably explained by a different weekly frequency of the training. Similarly, Petajan et al. [27] found in a group of 21 MS patients (EDSS ≤ 6) a 9.1% improvement of peak workload after 5 weeks and an 18.6% improvement after 10 weeks of aerobic training (15 weeks' programme, 3 times/week). A similar rehabilitation programme was designed by Rampello et al. [28]. They achieved a 10% improvement of W_{max} (82 ± 43 W vs. 103 ± 48 W) and a 20% improvement of $VO_{2max}.kg^{-1}$ (17.1 ± 7.1 vs. 20 ± 6.6 $ml.min^{-1}.kg^{-1}$) after 8 weeks (3 times/week) of training (11 MS patients, EDSS 3.5). Mostert and Kesserling [29] refer a 12% improvement of VO_{2max} after 4 weeks of training intervention (5 times/week, 30min bicycle ergometer).

A possible explanation of different results between the lower values of our study and the above-mentioned ones may probably be in a different design of the aerobic training on the bicycle ergometer. We used the interval training form in 70 % of the patients. The interval training form is generally considered rather as an alternative form of training and is preferred in patients with lower workload tolerance. In this kind of training, the workload phase alternates with a phase without any load or one with a lower intensity load. In our study, 30 seconds of the workload with the intensity at the level of anaerobic threshold alternated with 60 seconds with the intensity at the level of 5 to 10 Watts. This type of training produces only a minimum amount of lactate. At our department, continuous training has usually been used for patients with a higher cardiorespiratory capacity. Differences of the results (W_{ANP}, $W_{ANP}.kg^{-1}$) of the above-mentioned training programmes could also be caused by the use of different exercise protocols (interval vs. continuous training).

Muscle force

A comparison of the entrance and final 1-RM test values showed significant improvement in all of the tested exercises after programme completion. The highest strength was noticed in pulldown (21.9 %) and bench press (20.6 %) exercises, which are predominantly focused on shoulder muscle groups. Schwidt et al. [30] demonstrated a greater effect in upper extremity strength than in the lower extremity in MS patients. Similarly, in our study we found only a 14% increase of lower extremity muscle strength in comparison with upper extremity muscle strength (pulldown 21.9 %, bench press 20.6 %). In our previously reported pilot studies (23, 24, 25) in a group of 6 MS patients (EDSS 4.3 ± 1.0), we noticed a statistically significant increase of muscle strength only in the upper extremities. We suppose that MS patients should profit to a greater extent from a specific lower-extremity resistant training programme. This type of exercise training should have priority in designing a rehabilitation programme. White et al. [31] even recommend incorporation of the resistant training before an aerobic training.

In our group of patients, only 2 of the patients were able to follow the scheme of a 10 % weekly increase of 30–60 % 1-RM. The majority of them did not achieve even a 60% level of the resistant training intensity increase. This probably indicates a low tolerance and low capacity of MS patients for progression in resistant training. Therefore, the period of the rehabilitation programmes focused on lower-extremity resistant training should be prolonged.

Autonomic cardiovascular control

There were not found any signs of autonomic nervous system dysfunctions in the life history of the group of patients examined. A comparison of the HRV results with normative values of healthy population showed a significant decrease in all of the spectral bands [14]. Nevertheless, we did register a statistically insignificant increase in LF and HF

spectral powers and in Total Power in comparison with the initial values. Spectral analysis of heart rate variability is often used for monitoring and evaluating the rehabilitation therapy effect. On the basis of our experience with similar types of training programmes in patients with Ischaemic Heart Disease [32], Myocardial Infarction [34], or Hypertension [33] we consider the increase in HRV spectral powers as a sign of improving adaptability of autonomic cardiovascular regulation.

Programme safety, negative symptoms, and programme duration

We noticed only a slight exacerbation of neurological signs (hemiparaesthesia, visual worsening) in two cases because of a light asymptomatic viral infection in combination with the exercise training load. One week of home rest without any specific pharmacotherapy was recommended by the supervising neurologist. One patient (spastic paraparesis, 2 points of the Asworth scale) reported a temporary increase of lower extremity spasticity. It was expressed as acral clonus and worsening of the tibialis anterior muscle spasticity. No other patient was urgently forced to interrupt the programme. On the contrary, Rampello et al. [28] presented in their 8 weeks' study a 26% loss of the included patients (MS exacerbation, social status change, etc.). We did not notice any discomfort during the training on ergometers but nearly 70% of the patients reported myofascial or light postural disturbances requiring simple chiropractic interventions caused by the exercises for muscle strengthening. Similar findings were reported by Dodd et al. [32]. The maximal fatigue increase was reported between the 2nd and 3rd weeks of the programme, probably due to an adaptive physiological response to the workload of the exercise. There were not noticed any signs of overtraining. We decided to choose 8 weeks of the training programme on the basis of our experience with the same training design in cases of Ischaemic Heart Disease, Diabetes Mellitus, Myocardial Infarction, and Obesity (36, 37). Eight weeks of the exercise training programme in combination with the aerobic and resistant training forms realised twice a week are, according to the previously reported articles (27, 29, 31, 38, 39, 41, 42, 43), the shortest rehabilitation programme to record improvement in the physical fitness of MS patients.

CONCLUSION

The results of our study demonstrate a possibility of influencing some of the physical fitness parameters after 8 weeks of the rehabilitation programme realised twice a week with a combination of the aerobic and resistant training forms in a group of MS patients with mild to moderate clinical disability (EDSS 2.8 ± 0.7). The selected design of exercise training load significantly improved parameters of physical capacity (W_{SL}, $W_{SL}.kg^{-1}$), aerometabolic parameters (VO_{2SL}), extremity muscle strength (1-RM bench press, pulldown, leg extension), and self-perceived fatigue (MFIS, MFISp). We did not notice any significant changes in clinical disability (EDSS) and functional independence. We consider the increase in HRV spectral powers after exercise training as a sign of improving adaptability of autonomic cardiovascular regulation.

We also consider that the 8-week rehabilitation programme with a combination of the aerobic and resistant training forms should be safe for MS patients with mild to moderate clinical disability. It is essentially important to prescribe an individual intensity of the training workload with respect to the actual medical condition. The combined training programme seems to be safe for the MS patients with this level of disability.

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CARDIOVASCULAR PARAMETERS AND BAROREFLEX SENSITIVITY IN PARKINSON'S DISEASE

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INTRODUCTION

Symptoms of autonomic nervous system (ANS) dysfunction are an inseparable part of Parkinson's disease (PD). These non-motor symptoms have been increasingly recognised as a significant cause of morbidity in later stages of PD [49]. Recently, ANS dysfunctions have been extensively studied by many authors. Most of them, in relation to the method used, declare progression of ANS dysfunction proportionally to the progression of other motor symptoms of PD or to the disease duration (13, 34, 35, 41, 51, 66). Some of them declare autonomic failure even before the occurrence of the first motor symptoms (20, 48, 55). However, hardly any double-blind, randomised, controlled studies are available (59).

Clinical studies evaluate ANS function by standard tests, which are often based on examination of cardiovascular functions. This is substantiated by the fact that impairment of these functions accompanies the whole course of the disease and cardiovascular failure is one of the most common causes of death in PD patients [18].

The most common ANS tests include orthostatic test (15, 35, 43, 51, 63, 70); Valsalva manoeuvre (13, 15, 18, 66), isometric workload test (66); 30:15 ratio – the ratio between the increase of the heart rate (HR) at the 15th heart action and the decrease of HR at the 30th heart action after standing up from supine position [8]; E:I ratio – the ratio between the longest RR interval during expiration and the shortest RR interval during inspiration [18]; evaluation of the HR and blood pressure (BP) response to a deep breathing (13, 18, 47, 66); tilt table test (8, 15, 35, 52), test of hyperventilation (11, 15, 47); cold pressor test [15], sympathetic skin response (6, 8, 15, 19, 77), test of skin wrinkling [16], etc.

The evaluation of the degree of ANS dysfunctions is still in the forefront of research interest (1, 8, 13, 16, 34, 42, 73). The preceding studies, however, do not deal with differences in factors like severity of PD disability, type of dopaminergic and other pharmacotherapy (56, 57, 66, 67). Examination of heart rate variability (HRV) and baroreflex sensitivity (BRS)

lies among non-invasive methods with high sensitivity, validity, and reproducibility [29] that can declare ANS dysfunction in early stages of the disease (13, 18, 20, 22, 34, 39, 54, 60). Baroreflex is one of the most powerful short-term control mechanisms of arterial blood pressure.

Some authors also recommend BRS examination for differential diagnostics of PD and other extrapyramidal syndromes (6, 12, 15, 18).

The decrease of autonomic control of heart activity is a natural process caused by aging. However, age is not the only factor to cause this decrease of ANS activity (21, 65). A correlation of ANS dysfunction with the duration and especially progression of PD was declared repeatedly in many previous studies (13, 66, 18, 45, 74). On the contrary, the most recent studies based on iodine–131-meta-iodobenzylguanidine (MIBG) uptake in myocardial scintigraphy do not support this hypothesis and find no correlation between age, disease duration, and progression (62). Furthermore, a recent study by Haensch et al. [25] with the use of MIBG gives evidence that cardiac denervation occurs also in cases of absent orthostatic hypotension and impaired heart rate variability in PD.

The theory of antiparkinsonian pharmacotherapy as the other main factor of ANS dysfunction cause was also disproved. ANS dysregulation was also declared in studies with de novo PD patients before the first use of antiparkinsonian pharmacotherapy (5, 21, 25, 31, 39, 47). Nevertheless, the type of treatment should be analysed with respect to the aim of the study and correctly interpreted. There is wide evidence about modification of cardiovascular responses by levodopa, bromocriptine, selegiline, etc. (10, 14, 23, 33, 40, 56, 57, 66, 67, 72).

Another important factor with great impact on ANS function is the psychosocial status and cognitive impairment, especially depression (11, 38), dementia [30], apathy, anhedonia, etc. (53, 78).

AIM

The aim of the present paper was to study BRS and to analyse the relation between the progression of clinical impairment of PD and changes of blood pressure control by the baroreflex mechanism.

DESIGN AND METHODS

Altogether, 45 patients with idiopathic PD were recruited for the study from the Czech society "Společnost Parkinson o. s.", which organises regular exercise therapy for its members at a frequency of 1–2 times a week. Their diagnosis of idiopathic Parkinson's disease was confirmed at the 1st Department of Neurology, St. Anne's Faculty Hospital in Brno, according to the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria for Parkinson's disease [16].

Altogether 25 out of 45 patients who were recruited for the study did not fulfil the entrance criteria due to serious comorbidities (st. p. acute myocardial infarction, hypertension, diabetes mellitus), medication (antiparkinsonian pharmacotherapy with proved effect on cardiovascular function, antidepressants), depression, or the presence of any other exclusion criteria as listed above.

In total, 20 patients (12 men, 8 women) were included into the study. We evaluated their Body Mass Index (BMI).

They fulfilled the following entrance criteria: confirmed diagnosis of idiopathic PD according to the above-mentioned criteria; stable medication without any change for at least 4 weeks before BRS examination; no pharmacotherapy with proved effect on ANS or circulatory functions (4, 7, 10, 14, 23, 27, 28, 33, 40, 56, 57, 66, 67, 72); no serious comorbidities with impact on cardiorespiratory and ANS functions; non-smokers; no history of any cardiovascular diseases or abnormal ECG; no depression according to the Montgomery Asberg Depression Rating Scale [44].

Clinical examination of the Unified Parkinson's Disease Rating Scale (UPDRS) was used for the evaluation of the motor status – UPDRS III (range from 0 points: no motor complications, up to 56 points: maximum motor complications), late motor complications – UPDRS IV (range from 0 points: no late motor complications, up to 23 points: maximum late motor complications), and clinical impairment – UPDRS V (stage from 0: no impairment, up to 5: maximum impairment). The questionnaire method was used to assess the ANS status – SCOPA AUT. BRS was examined non-invasively as described in detail below. The basic characteristics of the examined group of patients are given in the table below ($\bar{\chi}\pm$ SD; Table 1):

Table 1:
Basic characteristics of PD patients

PD (n = 20)	AGE (years)	DURATION OF DISEASE (years)	BMI
$\bar{\chi}$	70.9	6.0	26.4
SD	6.3	3.0	2.3

A group of age- and sex-matched control subjects (CONTROL) was examined to enable a comparison of the absolute values of BRS. All the patients in this group fulfilled the entrance criteria as specified above for PD patients. The basic characteristics of the CONTROL group are given in the table below ($\bar{\chi}\pm$ SD; Table 2):

Table 2
Basic characteristics of healthy patients – controls (C)

C (n = 11)	AGE (years)	BMI
$\bar{\chi}$	69.9	28.0
SD	9.9	3.3

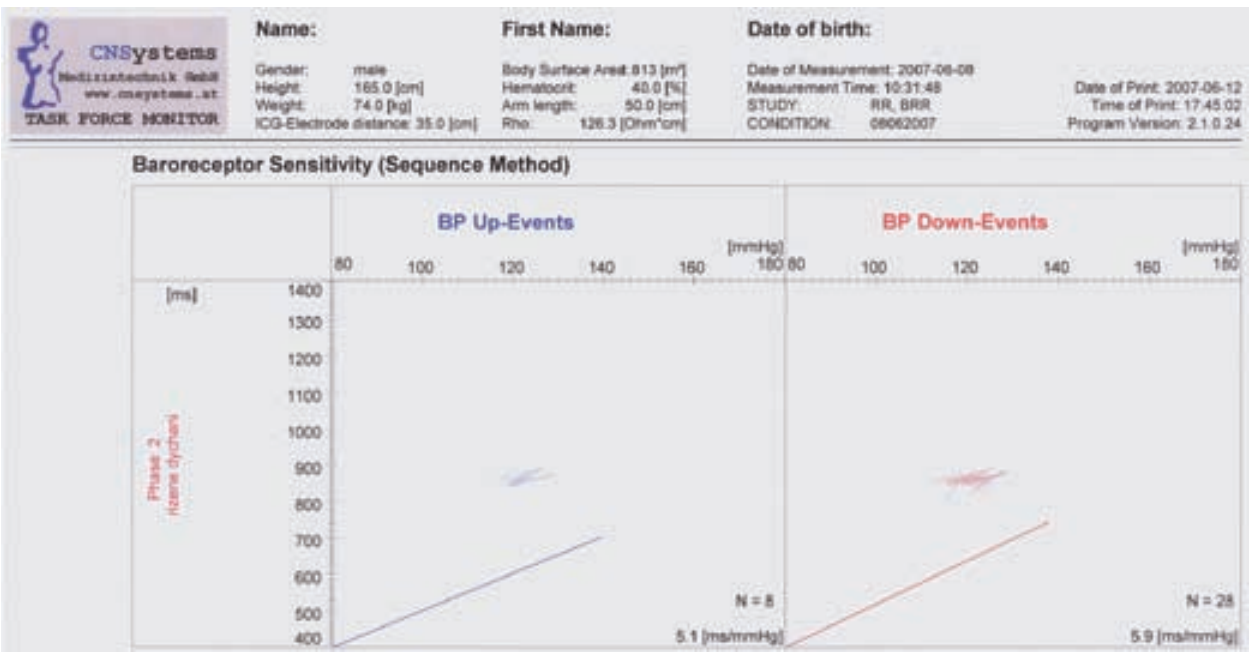
The assessment of BRS was based on non-invasive short-term examination (5 minutes) in the supine position at rest using the sequence method of analysis by the system Task Force Monitor, CNSystems Medizintechnik GmbH. The following criteria were fulfilled: no abnormal physical activity on the day before examination; at least 6 hours of sleep during the night before examination; good quality of sleep (score 6 or higher on the quality of sleep scale from the worst sleep, "0", to the best sleep, "10"), observance of the typical schedule of daily tasks including medication; only a light breakfast before examination without coffee, tea, alcohol (58), taking into account the age of patients – at least 2 hours before the examination; the ideal "on" state during examination [18]; examination on a working day between 9 and 11 a.m. to minimise the effect of circadian variations [37].

The data for the analysis were obtained from beat-to-beat measurement of blood pressure and heart rate. BRS was assessed from sequences of examination where there was an increase or decrease of systolic blood pressure (SBP) at least in 3 successive RR intervals. The threshold value for including measured beat-to-beat SBP and RR interval changes in a sequence was set at 1 mmHg for SBP changes and 6 ms for RR interval changes. The slope of the regressive curve based on the relation between SBP and RR interval expresses the baroreflex heart rate, shortly baroreflex sensitivity ([ms/mmHg]; 9, 36, 37).

Metronome-controlled breathing at a frequency f = 0.33 Hz (13, 24, 41, 47, 50, 54, 64, 66, 75) was used to increase the reproducibility of BRS examination. A graphic example of BRS sequence analysis examined in supine position at rest with metronome-controlled breathing (f = 0.33 Hz) is given in the graph below (Graph 1).

The measurement took place in a quite room. The subjects were examined after at least 10 minutes of resting in supine position with spontaneous breathing.

The absolute values of baroreflex (ms/mmHg) were considered as an indicator of the extent of cardiovascular ANS regulation impairment in all the cases where the number of sequences was sufficient (down-events ≥ 7 and up-events ≥ 7)



Graph 1
A graphic example of BRS examination results (V grafu 1 uvnitř nahradit svislou červenou popisku "Phase: 2 řízené dýchání" popiskou "Phase: 2 controlled breathing")

Table 3
Characteristics of patients in groups PD I, PD II, and healthy subjects C

	AGE (years)	DURATION OF DISEASE (years)	BMI	SPONTANEOUS BREATHING FREQ. (Hz)
C (n=11)	69.9±9.9	--	28.0±3.3	0.28±0.05
PD I (n=11)	70.7±7.2	5.1±2.7	26.8±2.7	0.32±0.03
PD II (n=9)	71.0±4.9	7.2±3.0	26.0±1.4	0.32±0.04
	n. s.	**n. s.**	**n. s.**	**n. s.**

Table 4
The results of Unified Parkinson's Disease Rating Scale (UPDRS): motor status – UPDRS III, late motor complications – UPDRS IV, clinical impairment – UPDRS V, and a questionnaire enquiry for the ANS dysfunction status SCOPA-AUT

	UPDRS III	UPDRS IV	UPDRS V	SCOPA-AUT
PD I (n=11)	19.8±10.0	3.7±3.2	1.7±0.5	15.0±8.1
PD II (n=9)	25.0±8.8	4.0±2.4	2.3±0.5	21.4±6.6
	n. s.	**n. s.**	**** p ≤0.01**	**n. s.**

Table 5
Examination results: haemodynamic parameters and BRS

	RR interval (ms)	SBP (mmHg)	DBP (mmHg)	BRS ms/mmHg
CONTROL (n=11)	72.6±13.0	127.7±11.1	78.3±9.5	7.7±3.6
PD I (n=11)	69.0±9.5	127.7±10.6	83.2±8.3	4.7±1.4
PD II (n=9)	64.8±8.7	118.3±7.5	76.2±8.6	--
	n. s.	**n. s.**	**n. s.**	**** p ≤0.01**

(the group of patients PD I). The patients with an insufficient number of sequences (down-events ≤ 7 and up-events ≤ 7) were grouped in PD II.

The differences in all the parameters examined were evaluated statistically. The normality of data distribution was tested by the Kolmogorov-Smirnov test and the differences between groups PD I and PD II by the *t*-test for independent samples (STATISTICA, StatSoft, Inc. 2008, v. 8.0).

The study was approved by the Ethical Committee of Masaryk University. All the patients were informed about the examination method used and their rights in relation to this study.

RESULTS

The results of the comparison of both groups of PD patients (PD I vs. PD II) are given in the tables below ($\bar{\chi}\pm$ SD, statistical

significance). In Table 3 there are values of age, duration of the disease, BMI, and frequency of spontaneous breathing ($\bar{\chi}\pm$ SD, statistical significance; Table 3):

In Table 4 there are values of the motor status UPDRS III, late motor complications UPDRS IV, the basic measure of clinical impairment UPDRS V, and a questionnaire enquiry for the ANS dysfunction status SCOPA-AUT ($\bar{\chi}\pm$ SD, statistical significance; Table 4):

A statistical comparison of the values of UPDRS V reveals a significant increase in PD II group defined as a group with an insufficient number of sequences in BRS examination. A comparison of the values of other parameters – UPDRS III, UPDRS IV, and SCOPA-AUT shows only an insignificant increase in PD II group.

In the following table the mean values of RR interval, systolic blood pressure (SBP), diastolic blood pressure (DBP), and BRS are presented ($\bar{\chi}\pm$ SD, statistical significance; Table 5):

A statistical comparison of the parameters chosen: RR interval, SBP, DBP, and BRS between groups PD I, PD II, and CONTROL revealed insignificant differences in the values of RR interval, SBP, and DBP. BRS was significantly lower in PD I group defined as a group with a sufficient number of sequences in BRS examination in comparison to the CONTROL group.

DISCUSSION

Baroreflexes are continuously activated by small deviations of arterial pressure around the set point. Spontaneous fluctuations of arterial pressure and RR interval can therefore express the quality of cardiovascular control mechanism [37].

BRS measurement plays an important role in the evaluation of cardiac ANS neuropathies in cardiovascular diseases as well as in neurodegenerative diseases. The mechanism of baroreflex is active during sudden changes of blood pressure and in the steady state as well. For that reason BRS activity can be also evaluated by an analysis of spontaneous fluctuation of arterial SBP and RR interval under various determined conditions in steady state (18, 36, 37).

Current research studies declare sympathetic noradrenergic dysfunction in PD patients. Its clinical importance is based on the fact that this dysfunction is considered to lead to orthostatic hypotension. The incidence of orthostatic hypotension is among 20–50 % of PD patients and is of major interest on account of its substantial participation on falls and accidental injuries (20, 42, 63). There was a 25% incidence of orthostatic hypotension in our group of PD patients.

There are other factors besides baroreflex that have an impact on heart rate variability during breathing. These factors influence the correlation between RR interval fluctuations and oscillations of SBP that is caused not only by baroreflex but also by respiration itself [4]. Nerve links in CNS cause an excessive transfer of the signal from the centre of respiration to medullary vagal efferent neurons, which results in an inhibition of the vagal activity during inspiration [47]. HR fluctuations are also dependent on the local intracardial or sinnodial stretch reflex [32]. Another reflexes with impact on HRV are the Hering-Breuer reflex (stimulated by lung and thoracic wall expansion during inspiration) and the Bainbridge reflex (increase of central venous volume causes changes in cardiac filling). Both of them stimulate cardiopulmonary structures mechanically and thus increase HR [47]. Humoral substances (e.g. angiotensin) also play an important role in the central modification of baroreceptor responses. All these factors can be influenced by different patterns of breathing, exercise, psychological stress, etc. [37]. We consider BRS examination with metronome-controlled breathing at a frequency of 0.33 Hz to be a method which decreases the impact of the above-mentioned factors and increases the reproducibility of BRS examination.

The results of the present paper support the theory of progression of ANS dysfunction on the basis of BRS examination from 5-minute recording during metronome-controlled breathing at a frequency of 0.33 Hz. Decreased numbers of UP and DOWN events were found in cases of advanced PD.

The same results were reported by Oka et al. [46] and Friedrich et al. [18] on the basis of BRS examination of larger groups of PD patients (spontaneous breathing). Friedrich et al. obtained the same results with the use of trigonometric spectral analysis of BRS.

The BRS score 4.7±0.5 ms/mmHg in the case of our group PD II with initial PD with UPDRS V 1.7±0.5 is significantly lower than that of the CONTROL group. The same values of BRS for healthy controls were published by Tank et al. (94) for spontaneous breathing in supine position and the age category of 60–69 years (8±3 ms/mmHg). Szili Török et al. (68) published similar data on the basis of a study with 23 PD patients of mean age 65±9.3 years, UPDRS V 2.1±0.8, BRS 4.3±3.5 ms/mmHg, and a control group of age- and sex-matched healthy individuals of mean age 70±6.6 years and BRS 8.9±6.9ms/mmHg.

No correlation was found in our study between any of the UPDRS subscales, SCOPA AUT, and symptoms of autonomic dysfunction. A correlation between orthostatic hypotension and decreased values of BRS was presented by other authors (15, 18, 47). Idiaquez [30] suggests independent involvement and variability among PD patients. The same opinion is supported in the latest studies by Shibata (62) based on MIBG myocardial scintigraphy.

ANS impairment is often less appreciated than motor impairment but is an important source of disability and handicap for many PD patients (71, 76). Management of non-motor symptoms should definitely be part of a comprehensive rehabilitation approach to the treatment of PD.

BRS examination also plays an important role in relation to the most common cause of death in PD. Increased mortality in PD patients is mainly due to respiratory and cardiovascular complications (2, 3). The ATRAMI study in patients after myocardial infarction showed that depressed BRS can be considered an independent predictor for sudden cardiac death (61).
We consider BRS examination as a valid tool for non-invasive assessment of ANS dysfunction in PD.

CONCLUSION

Advanced stages of PD are accompanied by more pronounced ANS dysfunction, which leads to a decrease of the number of sequences in BRS examination and to a decrease of the absolute values of BRS (4.7±1.4 ms/mmHg in PD patients vs. 7.7±3.6 ms/mmHg in healthy controls).

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SPIROERGOMETRY BEFORE AND AFTER AMBULATORY EXERCISE TRAINING IN PATIENTS AFTER ACUTE MYOCARDIAL INFARCTION

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INTRODUCTION

To be able to evaluate correctly the peak values of oxygen intake (VO_{2peak}) and working capacity, we must know whether in the exercise test a sufficient metabolic load (full metabolic capacity utilisation) was achieved. The peak value of the respiratory exchange ratio (RER_{peak}; ratio of CO_2 output to O_2 intake, indicated also as respiratory quotient), correlating with the increased lactate value and acidosis degree, is the criterion of the achieved level of metabolic load (full metabolic capacity utilisation) at submaximal and maximal load.
According to the Statement of the Working Group on Cardiac Rehabilitation and Prevention of the European Society of Cardiology the full metabolic loading is achieved at $RER_{peak} \geq 1.15$ and the exercise testing is valid [1].

AIMS

To assess the influence of respiratory exchange ratio RER_{peak} on VO_{2peak} validity in evaluation of the measure of improvement of maximal aerobic capacity of patients who suffered acute myocardial infarction after a 12-week controlled ambulatory rehabilitation programme.

MATERIAL AND METHODS

Study population

We evaluated 49 men incorporated into a 12-week controlled ambulatory rehabilitation programme. All patients suffered myocardial infarction (AMI) and started the rehabilitation programme within three months after AMI (Table 1). Acute myocardial infarctions were diagnosed at 1st Department of Cardioangiology in St. Anne's Faculty Hospital in Brno.
The patients were divided into two groups according to the achieved RER_{peak}. Group A reached $RER_{peak} \geq 1.05$; in group N

RER_{peak} < 1.05 (Table 1) was achieved in one or both exercise tests.

In the course of the rehabilitation programme all patients were symptomatically stable and their medication treatment was unchanged.

The whole study was carried out in accordance with the ethical principles of Helsinki convention from 1975 in the revision from 1983. All patients signed their informed consent.

Table 1

Characteristics of the examined set of patients with myocardial infarction

		Age (years) ($\bar{\chi}$± SD)	RER_{peak} ($\bar{\chi}$ ± SD) input	output
Group A	(n = 25)	61.3 ± 9.9	1.12 ± 0.04	1.15 ± 0.07
Group N	(n = 24)	57.8 ± 10.9	1.01 ± 0.06	1.10 ± 0.13

Rehabilitation programme

All patients went through a supervised exercise training with combined load three times a week for three months. The training unit consisted of a warm-up phase (10 min), an aerobic phase (25 min), a resistance training phase (15 min), and a relaxation phase (10 min).

The aerobic phase on bicycle ergometers (Ergoline REHA E900) consisted of a warm-up phase lasting 3 to 4 minutes at a low load, of a 25-min training with the intensity at the anaerobic threshold level given by spiroergometric examination, and of a 2-min cool-down phase during which the load intensity was gradually decreasing [2]. The resistance exercises made on multifunctional TK-HC COMPACT machines included bench press, pull down of the pulley, and leg extension; out of the machine sitting-lying was performed. The load intensity was determined by the 1-RM method (one repetition maximum, i.e. one repetition of the given exercise made in the full extent of the movement with maximal load) [3]. The individual exercises were made in 3 to 5 series, at 10 repetitions. During the whole training unit the following indices were monitored: heart rate, blood pressure, degree of subjective perception of the load intensity according to Borg scale; during the aerobic and resistance training phases ECG was also monitored.

Methods of examination

A symptom-limited spiroergometric examination with ventilator gas analysis was performed before the start and after the finish of the cardiovascular rehabilitation programme (98 examinations altogether). It was started by ECG monitoring at rest in lying and sitting position (Schiller CS 100). This was followed by 3-min adaptation in the sitting position on an ergometer. The workload was increased in one-minute intervals. The rate of the workload increase was chosen according to the supposed fitness in such a way that the total workload duration was 8 to 12 minutes. In the course of the exercise test ECG was monitored continuously, heart rate was recorded every minute according to ECG, manual blood pressure measurements and determination of the degree of subjective perception of the load according to Borg scale were made every 2 minutes. The test can be terminated because of dyspnoea, exhaustion, reaching of the limit heart-rate value (220-age), an abnormal hypertension reaction (≥ 230/115), decrease of systolic blood pressure (> 10 mmHg), indications of ischaemia on ECG, angina pectoris, substantial dysrhythmia, loss of motion co-ordination, disturbances of consciousness, pain, orthopaedic or neurological reasons, technical causes, etc.

Oxygen uptake, CO_2 output, and ventilation were measured in each breath (breath-by-breath analysis) and averaged values for 30 s were recorded in a printed report (device: Pulmonary Function System 1070 – MedGraphics, USA). The device determined automatically the anaerobic threshold according to the changes of the ventilation-respiratory values and, moreover, in all of them the determined anaerobic threshold was checked according to V-slope, by comparing the curves of the ventilation equivalent VE/O_2 and VE/CO_2, and the curve of CO_2 excess $[ExCO_2=((VCO_2)^2 / VO_2) – VCO_2]$.

The anaerobic threshold value was expressed as VO_2 and, for the need of physical training, in watts with the corresponding heart rate and degrees of Borg scale of subjective perception of the load intensity.

Statistical processing

Statistical processing was made by using the Microsoft Excel for Windows program and the Statistica program, version 6.1.

The distribution was evaluated by *Lillefors modification of the Kolmogorov-Smirnov test of normality* in the Statistica program. With regard to normal distribution, parametric tests were used. In comparing two dependent variables, a *two-sample paired t-test to mean value* (in the Microsoft Excel program) was performed. In comparing two independent variables, first of all it was found out by a *two-sample F-test for variances* whether the variances differed or not, and, as the case may be, either a *two-sample t-test with equality of variances* or a *two-sample t-test with inequality of variances* was used (all of them in the Microsoft Excel program).

In all the tests the significance level was primarily set to 0.05. If the result on this level was statistically significant, testing was also made on a significance level of 0.01, possibly 0.001. Invariably, double-sided testing was used. The results are presented in the form of means ($\bar{\chi}$) and standard deviations (SD).

Table 2
A comparison of the input and output values of VO_{2peak} and W_{peak} in individual groups of patients with MI

	VO_{2peak} ($ml.kg^{-1}.min^{-1}$)			W_{peak} ($W.kg^{-1}$)		
	Input	Output	Statist. sign.	Input	Output	Statist. sign.
Group A	21.3 ± 3.9	23.7 ± 4.4	$p < 0.01$	1.40 ± 0.33	1.64 ± 0.36	$p < 0.001$
Group N	19.6 ± 3.6	24.9 ± 6.3	$p < 0.001$	1.21 ± 0.33	1.72 ± 0.46	$p < 0.001$

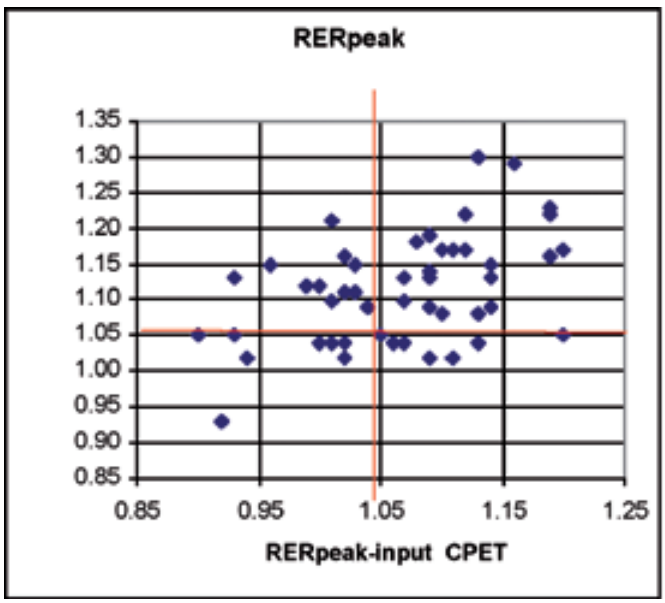
Table 3
A comparison of the differences of VO_{2peak} and W_{peak} between groups A and N of patients with MI

	Group A	Group N	Statist. sign.
VO_{2peak} ($ml.kg^{-1}.min^{-1}$)	2.4 ± 3.3	5.1 ± 5.3	$p < 0.05$
W_{peak} ($W.kg^{-1}$)	0.24 ± 0.24	0.51 ± 0.36	$p < 0.01$

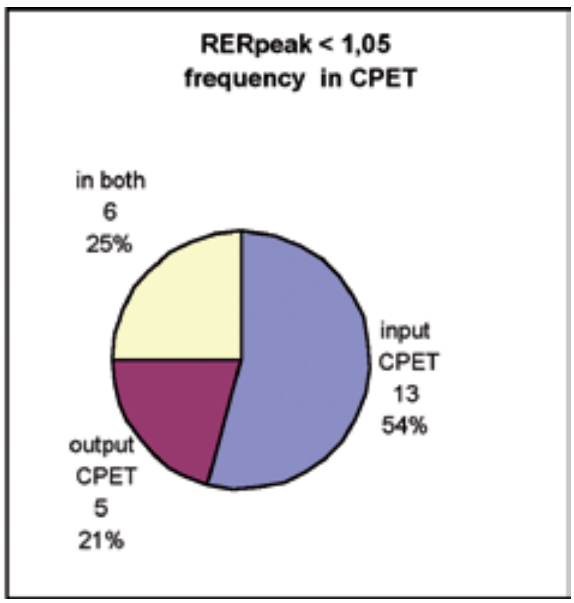
RESULTS

Graph 1 shows a survey of 98 spiroergometric examinations according to the value of RER_{peak}. In 25 patients $RER_{peak} \geq 1.05$ was achieved in both tests (right upper quadrant of Graph 1). In 5 patients only $RER_{peak} \geq 1.15$ was achieved and the value of VO_{2peak} can therefore be considered to be valid according to the Statement [1]. In 30 examinations $RER_{peak} < 1.05$, out of this in 13 patients in the entrance examination (left upper quadrant of Graph 1), in 5 patients in the final examination (right lower quadrant of Graph 1), and in 6 patients in both examinations (left lower quadrant of Graph 1). In the group with $RER_{peak} < 1.05$ low RER_{peak} predominated significantly in the entrance examinations (Graph 2).

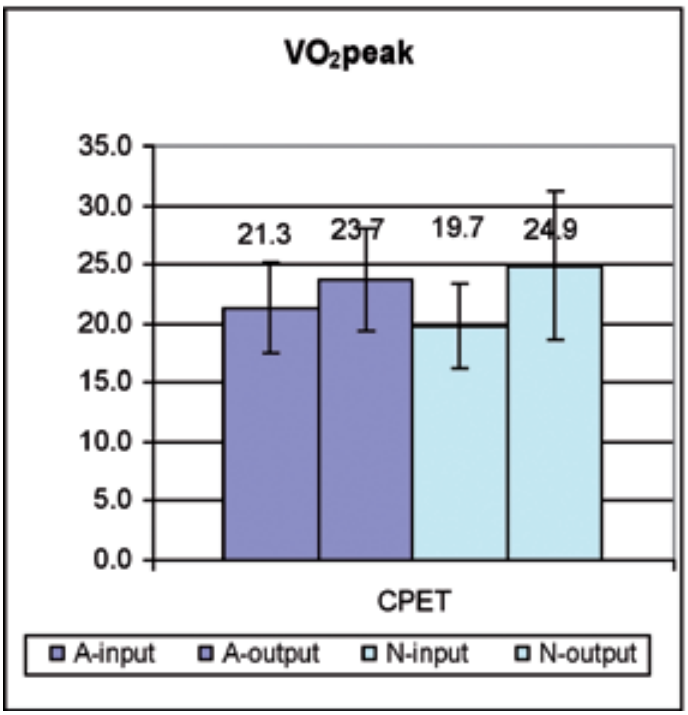
In these 30 exercise tests that were terminated prematurely ($RER_{peak} < 1.05$), only in one third were the symptoms indicating a possible limitation of the transport system (exhaustion, dyspnoea, angina pectoris) the cause of test termination.



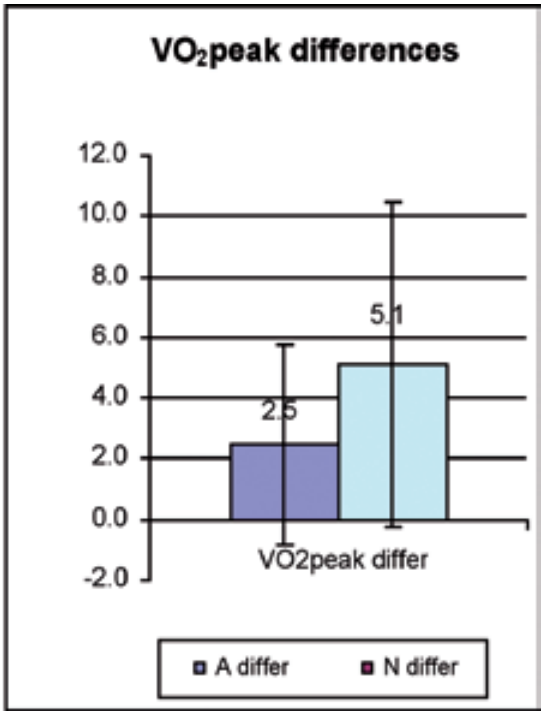
Graph 1
Spiroergometric examinations according to the value of RERpeak



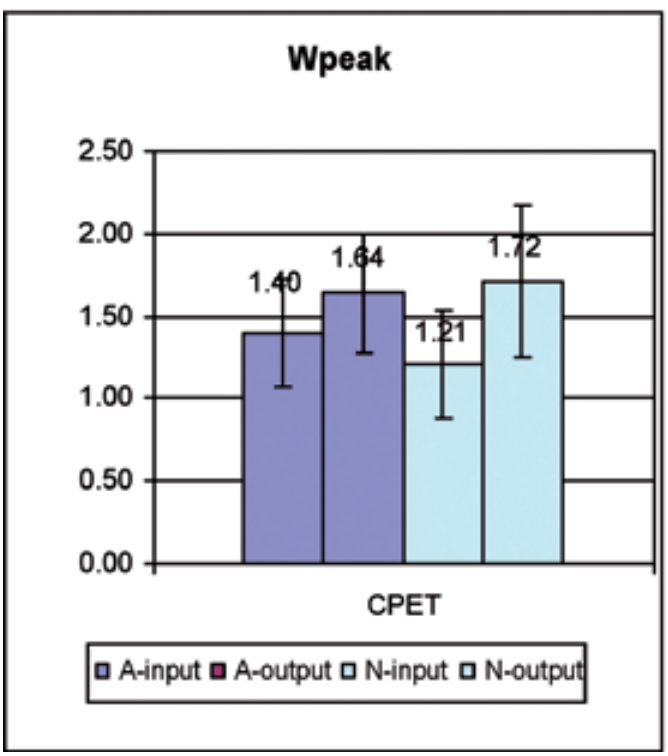
Graph 2



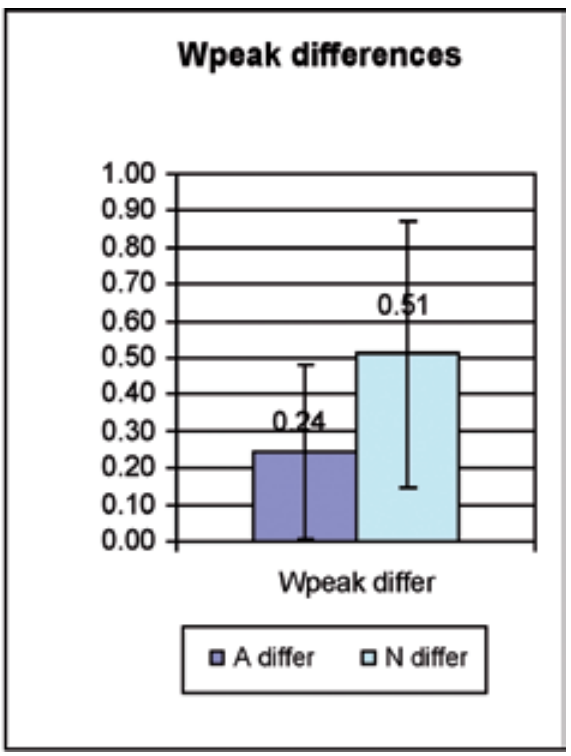
Graph 3



Graph 4



Graph 5



Graph 6

In group A the value of VO_{2peak} increased by 2.4 $ml.kg^{-1}.min^{-1}$ ($p < 0.01$) after the 12-week rehabilitation programme, and in group N the value of VO_{2peak} increased by 5.1 $ml.kg^{-1}.min^{-1}$ after the completion of the rehabilitation programme (Table 2, Graph 3). The value of the total achieved load (W_{peak}) increased in group A by 0.24 $W.kg^{-1}$ ($p < 0.001$) and in group N by 0.51 $W.kg^{-1}$ ($p < 0.001$) (Table 2, Graph 4). A comparison of the differences between groups A and N is shown in Table 3 and Graphs 4, 6.

DISCUSSION

The results of our preceding studies of men and women with IHD, included in the controlled rehabilitation programme within the framework of cardiovascular rehabilitation, showed that from the value of $RER_{peak} \geq 1.05$ the values of VO_{2peak} can be considered to be acceptably valid for the purpose of comparison of exercise tests (4, 5). That is why we divided this set of men after AMI in advance into groups A and N. If the achieved value of $RER_{peak} < 1.05$, then VO_{2peak} will be underestimated and thus a mistaken assessment of VO_{2peak} differences and distorted results in evaluation of the dynamics of the changes can occur. It also turned out in the results of this study; lower input values of VO_{2peak} had a significant share in more than a twofold increase of VO_{2peak} in group N in comparison with group A in the premature termination of the exercise test with subsequent increase of the difference between the entrance and final tests. Similar changes were also detected in the analysis of W_{peak} both in group A and N.

It is apparent that the knowledge of RER_{peak} value is necessary for the correct interpretation of peak values (VO_{2peak}, W_{peak}, etc.). RER_{peak} value is also important for the correct classification into functional classes according to VO_{2peak} (e.g. according to Weber). With regard to the fact that the study is not a mortality one, we cannot express our opinion of VO_{2peak} validity for assessment of the prognosis (at RER_{peak} in a range of 1.05 to 1.14). The values of VO_{2peak} achieved at $RER_{peak} < 1.00$ have no longer prognostic significance [6].

CONCLUSION

When comparing two and more exercise tests, the achievement of a sufficient and comparable metabolic loading in both tests is a precondition of the correct evaluation of the dynamics of changes; RER_{peak} value in both tests should be at least 1.05. Low values of RER_{peak} indicate premature termination of the exercise test and, consecutively, low, underestimated values of $VO_{2peak.}$ In comparing two exercise tests with considerably different RER_{peak}, the values of VO_{2peak} and thus also the difference of peak values of oxygen intake are significantly influenced. At a low input RER_{peak} the difference of VO_{2peak} increases (apparently a considerable improvement), at a low output RER_{peak} the difference contrarily decreases (apparently a small or no improvement of VO_{2peak}). According to the results of our study, premature termination of the symptom-limited exercise test is relatively frequent. In men with IHD, RER_{peak} is lower than 1.05 (4, 5) in as many as 40 %.

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DIFFUSED INTIMA-MEDIA THICKNESS REGRESSION AFTER 20 MONTHS OF PRAVASTATIN 40 MG TREATMENT: A CASE REPORT

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ABSTRACT

Cardiovascular disease is a dominant cause of global death, and atherosclerosis is its pre-eminent precursor, which begins with the loss of endothelium integrity, increased permeability to atherogenic lipoproteins and other pathological phenomena which result in intima-media thickness increase. We describe the case of a 48-year-old woman affected by heterozygous familial hypercholesterolemia and recurrent vulvovaginal candidiasis episodes, periodically treated with oral fluconazole; while she did not use to take any drug for lower total-cholesterol and LDL-cholesterol. After 20 months of therapy with Pravastatin 40 mg daily, we noted an evident regression of diffused intima-media thickness in all vascular districts probed by ultrasound technique. We claim the importance and efficacy of Pravastatin therapy at the full dosage to normalise the lipidemic profile and to slow down the atherosclerosis progression, as has just been demonstrated by a simple and safe diagnostic image technique.

INTRODUCTION

Cardiovascular disease is a leading cause of death in the world and it is recognised as a multifactorial pathology with different sources of risk [1]. The atherosclerotic process consists of several and complex pathological phenomena, such as intima-media thickness increase, leading to a higher risk of cardiovascular events. High plasma concentration of low-density lipoprotein-cholesterol (LDL-c) is one of the principal factors which promote the progression of atherosclerotic disease [2]. Several genetic and environmental factors can induce lipid disorder. A hyperlipidemic condition can be the result of a single gene or a polygenic deficiency in a metabolic pathway of lipoproteins, or it can be the consequence of several other pathological conditions, such as hypothyroidism, diabetes mellitus, renal disease, hepatic disease, and others [3].

Table 1
Comparison between intima-media thickness measurements before and after 20 months of therapy with Pravastatin 40 mg daily.

	Left CC	Right CC	AA	Right IA	Left IA	Right FA	Left FA	Right RA	Left RA
1°IMT values*	0.9 mm	1.0 mm	1.3 mm	2.4 mm	1.1 mm	1.1 mm	1.2 mm	1.2 mm	1.3 mm
2° IMT values^	0.9 mm	0.8 mm	0.9 mm	2.0 mm	1.0 mm	0.9 mm	0.8 mm	0.6 mm	0.9 mm

* before starting Pravastatin therapy
^ in the course of Pravastatin therapy
IMT : Intima-media thickness; CC: Common carotid; AA: Abdominal aorta; IA: Iliac artery; FA: Femoral artery; RA: Renal artery.

THE CASE

A 48-year-old woman, non-smoking, with normal blood pressure values, not in excess weight (body mass index = 23.8) and following a diet poor in saturated fats, presented to our clinic with a persistent alteration of lipid assessment. The patient had a history of recurrent vulvovaginal candidiasis, periodically treated with oral fluconazole. Her previous laboratory examinations showed that the mean value of total cholesterol (TC) was 350 mg/dL, of LDL-c was 270 mg/dL, of high density lipoprotein-cholesterol (HDL-c) it was 45 mg/dL, and of triglycerides it was 180 mg/dL. For a correct diagnosis and an appropriate cardiovascular risk evaluation we suggested other in-depth blood tests and an ultrasound colour Doppler probing of carotid-vertebral-basilar, aortic and iliac-femoral districts with a morphological assessment. The ultrasound examination showed a diffused intima-media thickness increase (max. thickness = 1.3 mm in abdominal aorta; 2.4 mm in right iliac artery; 1.1 mm in left iliac artery; 1.1 mm in right femoral artery; 1.2 mm in left femoral artery; 1.2 mm in right renal artery; 1.3 mm in left renal artery; 0.9 mm in right common carotid; 1.0 mm in left common carotid) with some rosary-like pattern of lesions. The rest of the laboratory studies, including the coagulation profile, inflammatory indexes, kidney and liver functional parameters, were in normal range. According to her history and laboratory results, we diagnosed a form of heterozygous familial hypercholesterolemia and prescribed a therapy with Pravastatin 40 mg tablets once a day. The patient had not taken any lipid-lowering medication before. We opted for Pravastatin therapy to reduce at the most the possible interaction with fluconazole cyclic administration.

After two months of treatment a decrease of TC and LDL-c was noted. This decrease was confirmed in the following laboratory controls, which showed, after 20 months of therapy, a decrease in TC of 43 %, in LDL-c of 55.6 %, and in TG of 11.4 % from baseline, and an increase in HDL-c of 6.3 % from baseline. After 20 months of treatment, we also ordered a new ultrasound colour Doppler control to monitor intima-media thickness. The ultrasound study was performed by the same operator who had performed previous controls. A remarkable regression of intima-media thickness in the arterial districts previously examined was described in a detailed report (max. thickness = 0.9 mm in abdominal aorta; 2.0 mm in right iliac artery; 1.0 mm in left iliac artery; 0.9 mm in right femoral artery; 0.8 mm in left femoral artery; 0.6 mm in right renal artery; 0.9 in left renal artery; 0.7 mm in right common carotid artery; 0.7 mm in left common carotid artery) (*Table 1*). After 3 months the data reported in Table 1 were confirmed by another ultrasound examination performed by the same operator.

DISCUSSION

Atherosclerosis is a long-term pathological process characterised by continuous deposition of modified lipids and growth of arterial walls, starting with fatty streaks in childhood and ending with complicated lesions which block the blood flow, inducing severe clinical symptoms. High plasma concentration of LDL-c is one of the principal factors that influence the progression of atherosclerotic disease [2]. In this report our patient was affected by a heterozygous form of familial hypercholesterolemia, an autosomal dominant disorder caused by a mutation in the gene encoding for LDL receptor protein. While the extremely rare homozygous form is characterised by two mutant alleles encoding for LDL receptor locus, the heterozygous carriers have a normal allele that provides one half of the normal receptor activity. Heterozygous familial hypercholesterolemia affects approximately 0.2 per cent of the global population [4]. We advised our patient to take the Pravastatin drug (40 mg daily), a hydroxyl-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor. Pravastatin does not interact with azolic antifungal drugs and is effective in lowering TC and LDL-c serum levels and, above all, in preventing coronary heart events by slowing down the atherosclerotic process. The magnitude of this effect is primarily due to

LDL-c decrease but it may be related to other lipid parameter modifications, and to additional anti-inflammatory properties of this drug [5–6]. MacMahon et al. demonstrated, in a LIPID study, that Pravastatin therapy reduces the development of carotid atherosclerosis among patients with coronary heart disease; this treatment prevented any detectable increase in carotid wall thickening over four years of follow-up [7]. In clinical practice the intima-media thickness is considered a valid surrogate marker for the progression of atherosclerotic disease and a substitute end point of vascular outcomes in different trials [8–9]. The high-resolution b-mode ultrasound technique is one of the best methods to detect atherosclerotic damage, because it is rapidly applicable, not-invasive and easily available [10].

We presented this case report to confirm the beneficial effects of statin therapy on the lipid profile and intima-media thickness. Long-term treatment based on Pravastatin 40 mg daily administration was effective and safe. A considerable decrease of LDL-c serum levels was noted and a remarkable regression of intima-media thickness was detected by the ultrasound imaging technique, showing the importance and applicability of this diagnostic imaging method for a careful follow-up of patients.

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COMPLEX PARTIAL SEIZURE-LIKE SYMPTOMS AND SMOKING IN UNIVERSITY STUDENTS

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ABSTRACT

Complex partial seizure-like symptoms are believed to be a manifestation of mild temporolimbic dysfunction. The present study was undertaken to address the issue of occurrence of these symptoms in a healthy population and to investigate their relation to common psychopathology and smoking. The data analysed were collected during the year 2008 from 196 university students. Statistical analysis showed close association between seizure-like symptoms and symptoms of dissociation and distress. It was also shown that smokers (N 51) had a higher level of seizure-like symptoms than non-smokers (N 145). The implications of the finding for smoking cessation interventions are discussed.

INTRODUCTION

In recent neuropsychiatric research there has been a growing interest in the neurobehavioural syndrome characterised by multiple cognitive, affective, and psychosensory symptoms. Patients suffering from this disorder usually seek medical help for affective and mood complaints (anxiety, persistent dysphoria, ego-dystonic rage outbursts), concerns about "going crazy", transitory cognitive problems (memory gaps, brief confusion spells, frequent word-finding lapses), or complaints of atypical headache and cephalic pain. The anticonvulsant medication generally produces marked reduction in symptoms and improved affective status in spite of the fact that the patients lacked the customary diagnostic criteria of neurological seizure disorder. In Jonas [1], as a summary of his long-lasting clinical study, provided a detailed description of this syndrome under the label "subictal neurosis". More recently, Springer and colleagues [2] described such patients as manifesting an "epilepsy spectrum disorder" because many of their symptoms were presented in patients with temporal lobe epilepsy. Among researchers engaged in this field there

is an increasing belief that the temporolimbic dysfunction, represented by occasional spontaneous electrical discharges, underlies behavioural dyscontrol and affective dysregulation exhibited by these patients.

For the detection of the breadth and frequency of seizure-like symptoms, Roberts et al. [3] created a structured clinical interview (CPSI – Complex Partial Seizure-like Symptoms Inventory). With the aim to assess the possible genesis of these symptoms he compared a group of subjects with a history of an injury or illnesses capable of producing cerebral damage or dysfunction with normal controls who reported themselves to be free of cerebral disease, denied a history of closed head injury and any psychiatric treatment. The first group exhibited a fivefold higher mean CPSI score than healthy controls. A very similar set of symptoms was studied by Teicher et al. [4] in the context of neurobiological consequences of childhood maltreatment. It comprised various perceptual distortions, brief hallucinatory events, motor automatisms, and dissociation phenomena presenting always in the absence of clinical seizures. For their detection he created a questionnaire (Limbic System Checklist–33, LSCL–33). He found out that outpatients with self-reported history of physical or sexual abuse had increased LSCL–33 scores that were dramatically elevated in patients with a history of combined abuse, both physical and sexual [4]. Although these two authors hypothesised differently about the genesis of the underlying neuropathology of the syndrome, their idea about the generation of seizure-like symptoms was identical. Both considered the temporolimbic dysfunction to be the source of overall psychopathology of their patients.

The present study was undertaken to address the issue of occurrence of complex partial seizure-like symptoms in a population of healthy university students. A second goal of the study was to investigate the relationship between these symptoms and common psychopathology presented in the norm. Due to the assumed association between seizure-like symptoms and general psychopathology on the one hand and the known higher general psychopathology in smokers on the other hand [5, 6, 7, 8, 9, 10], we were also interested in the level of CPS symptoms in this group.

MATERIALS AND METHODS

Participants

The sample was recruited from healthy university students (153 males and 43 females; mean age 22.1 ± 1.9). It included 51 regular cigarette smokers (30 males and 21 females) who smoked 7 ± 6.2 cigarettes per day for 5.7 ± 3.6 years. Their mean score of the Cigarette Dependence Scale (CDS) was 31.2 ± 10.0. The exclusion criteria were organic diseases of the CNS, any form of epilepsy, psychiatric disorders, alcohol dependence, and drug abuse. The smoking criteria were based on Flay's evaluation [11], which defines smoking maintenance as a stage of regular use from occasional to daily smoking leading to the development of chronic, daily patterns of nicotine use. Smokers were allowed to smoke ad libitum according to their habits. The study was approved by the University ethical committee and all the participants gave their written informed consent.

Psychometric measurement

The occurrence of seizure-like symptoms was assessed by the Complex Partial Seizure-like Symptoms Inventory (CPSI) [3]. The CPSI was designed to measure somatic, sensory, behavioural, and memory symptoms associated with ictal temporal lobe epilepsy (brief hallucinations, paroxysmal somatic disturbances, automatisms, and dissociative disturbances) but also occurring in non-epileptic conditions (minimal score 0, maximal score 175; Cronbach's alpha 0.95, test-retest reliability after one week 0.87). The inventory has 35 questions and the subjects indicate the degree of their experience on a 6-point Likert scale. A total score higher than 70 meets the criterion for the so-called epilepsy spectrum disorder but also lower values may indicate an electrophysiological dysfunction [3].

For screening general distress and traumatic stress symptoms, a Trauma Symptom Checklist TSC–40 questionnaire [12] was used. The TSC–40 was developed to assess the adult symptom patterns associated with a history of victimisation, especially childhood sexual abuse, but it is also suitable for measuring general distress symptoms (minimal score 0, maximal score 120; Cronbach's alpha 0.91, test-retest reliability after one week 0.88). The inventory has 40 questions and the subjects indicate the degree of their experience on a 4-point Likert scale.

For the screening of depression, the self-reported Beck Depression Inventory (BDI-II) [13] was used (minimal score 0, maximal score 63; Cronbach's alpha 0.89, test-retest reliability after one week 0.85). The inventory has 21 items on a 4-point Likert scale. A score ≥10 has been suggested as a clinical cut point.

The anxiety symptoms were measured using a Self-reported Anxiety Scale (SAS) [14]. The inventory has 20 items on a 4-point Likert scale (minimal score 20, maximal score 80; Cronbach's alpha 0.81, test-retest reliability after one week 0.82).

The dissociation symptoms were measured by a Dissociative Experience Scale (DES) [15]. The DES is a self-report scale asking the respondents to indicate their response on a 100mm scale recording to what extent they experience 28 dissociative phenomena in their daily life (minimal score 0, maximal score 100; Cronbach's alpha 0.92, test-retest reliability after

Table 1
Descriptive statistics of mean scores of the questionnaires used, obtained from all the participants (N 196)

	Mean	SD	Median	Min.	Max.
CPSI	19.5	14.7	16.0	0.0	84.0
SAS	32.9	6.0	32.0	22.0	58.0
BDI_II	7.7	5.6	7.0	0.0	29.0
TSC_40	23.3	11.8	21.0	3.0	62.0
DES	8.8	8.7	5.8	0.0	46.8

Note: CPSI – Complex Partial Seizure-like Symptoms Inventory; SAS – Self-reported Anxiety Scale; BDI-II – Beck Depression Inventory; TSC–40 – Trauma Symptom Checklist; DES – Dissociative Experience Scale

Table 2
Correlation of mean scores between CPSI and the other questionnaires used (Spearman's correlation coefficient values)

	SAS	TSC_40	BDI_II	DES
CPSI	0.53*	0.62*	0.53*	0.74*

Note: CPSI – Complex Partial Seizure-like Symptoms Inventory; SAS – Self-reported Anxiety Scale; TSC–40 – Trauma Symptom Checklist; BDI-II – Beck Depression Inventory; DES – Dissociative Experience Scale; * – p<0.00001

Table 3
Intergroup comparison of mean scores of BDI-II, SAS, DES, and TSC–40 for participants with mean CPSI scores lower and higher than median

	Low CPSI (N=98) Mean ± SD	High CPSI (N=98) Mean ± SD	ANOVA	
			F	p
SAS	30.4 ± 4.6	35.4 ± 6.3	F(1. 194)=39.553	0.000001
BDI-II	5.4 ± 4.9	10.1 ± 5.2	F(1. 194)=42.806	0.000001
TSC–40	17.6 ± 8.8	29.2 ± 11.6	F(1. 194)=61.169	0.000001
DES	4.7 ± 3.9	12.9 ± 10.2	F(1. 194)=55.381	0.000001

Note: CPSI – Complex Partial Seizure-like Symptoms Inventory; SAS – Self-reported Anxiety Scale; TSC–40 – Trauma Symptom Checklist; BDI-II – Beck Depression Inventory; DES – Dissociative Experience Scale

one week 0.91). Examples of such phenomena include feelings of depersonalisation, derealisation, and psychogenic amnesia.

The nicotine dependence was assessed by the Cigarette Dependence Scale (CDS) [16]. This scale measures addiction to cigarettes in daily and occasional cigarette smokers (minimal score 12, maximal score 60). A twelve-item version was used in the present study (Cronbach's alpha 0.84, test-retest reliability after one week 0.83).

Statistical evaluation of the questionnaire scores was performed using the software package Statistica version 8.0. For statistical assessment of differences between the defined subgroups the analysis of variance (ANOVA) for independent samples was applied. In statistical assessment of relationships between the questionnaire scores Spearman's correlation coefficient was used.

RESULTS

As shown in *Table 1*, the range of complex partial seizure-like symptoms was in our sample of university students relatively large (scores from 0 to 84). It demonstrates that even in a healthy, non-clinical population the proportion of persons with a relatively high number of these symptoms is not negligible. This fact becomes especially significant in context with the demonstrated associations between the CPSI score

Table 4
Gender differences in scores of the questionnaires used

	Male (N=153) Mean ± SD	Female (N=43) Mean ± SD	ANOVA	
			F	p
CPSI	19.2 ± 14.4	20.5 ± 15.7	F(1. 194)=.24520	0.62
SAS	32.3 ± 5.1	35.3 ± 8.3	F(1. 194)=8.1313	0.005
BDI-II	7.7 ± 5.4	8.0 ± 6.4	F(1. 194)=.13478	0.71
TSC–40	22.4 ± 10.4	26.5 ± 15.6	F(1. 194)=4.0012	0.05
DES	8.5 ± 8.0	9.7 ± 10.7	F(1. 194)=.68877	0.41

Note: CPSI – Complex Partial Seizure-like Symptoms Inventory; SAS – Self-reported Anxiety Scale; TSC–40 – Trauma Symptom Checklist; BDI-II – Beck Depression Inventory; DES – Dissociative Experience Scale

Table 5
Differences in scores of the questionnaires used between smokers and non-smokers

	Non-smokers (N=145) Mean ± SD	Smokers (N=51) Mean ± SD	ANOVA	
			F	p
CPSI	17.6 ± 13.8	25.0 ± 15.8	F(1. 194)=9.9428	0.002
SAS	32.00 ± 5.76	35.41 ± 6.40	F(1. 194)=12.342	0.001
BDI-II	7.26 ± 5.75	9.31 ± 4.89	F(1. 194)=3.5754	0.06
TSC–40	21.82 ± 11.39	27.0 ± 11.41	F(1. 194)=7.0126	0.01
DES	8.01 ± 8.34	11.02 ± 9.48	F(1. 194)=4.6263	0.03

Note: CPSI – Complex Partial Seizure-like Symptoms Inventory; SAS – Self-reported Anxiety Scale; TSC–40 – Trauma Symptom Checklist; BDI-II – Beck Depression Inventory; DES – Dissociative Experience Scale

and customary distress psychopathology (see *Table 2*). The finding of highly significant differences in the mean scores of BDI-II, SAS, TSC–40, and DES between two subgroups of students created by division of the whole sample according to their median of the CPSI score (see *Table 3*) represented corroborating evidence of the relationship between the seizure-like symptoms on the one hand and the distress and dissociation symptomatology on the other hand. In gender comparison no significant difference in the CPSI score was found. The only gender significant difference was observed in SAS and TSC–40 scores; in both cases the ratings of women were higher. *Table 5* presents differences between smokers and non-smokers in the mean scores of the questionnaires used. Besides the well-known higher occurrence of anxiety, depression, and distress symptoms in smokers (SAS, BDI-II, TSC–40), this result revealed a new fact, i.e. that smokers have a higher rating of complex partial seizure-like symptoms in comparison to non-smokers.

Statistical analysis did not show any significant association between the cigarette dependence scale (CDS) and symptoms of depression, seizure-like symptoms, anxiety, distress, and dissociation.

DISCUSSION

The results of the present investigation revealed, in a sample of a non-clinical population, the existence of a relatively large subgroup of subjects with frequent seizure-like symptoms. In approximately 15 % of the participants the CPSI score was over 35. From correlations with other questionnaires it is evident that these persons will report at the same time more anxiety, depression and other distress symptoms, and more dissociation phenomena. As will be shown later, the possibility that general psychopathology can arise from temporolimbic dysfunction is of practical significance, for instance in considering the beginning and intervention of an abuse of nicotine. Consistent with the reports cited above, there may be two different ways leading to temporolimbic dysfunction. The first hypothetical aetiological chain is related to the existence of microscopic cerebral scars in the

temporal lobe, the rhinencephalon, and the thalamus due to trauma or minimal encephalitis following childhood diseases [1,3]. These minor structural changes are believed to lead to spontaneous electrical discharges producing then a variety of psychopathological manifestations. The second aetiological explanation takes into consideration a possible impact of early stress, which can produce a cascade of neurobiological events ranging from neurohumoral to structural and functional changes with the resulting temporal lobe or limbic seizure-like activity [17]. This development can be endured by the kindling process in which repeated intermittent neuronal stimulation produces an ever greater alteration in the excitability of the implicated structures, eventually resulting in spontaneous electrical discharges [18,19]. The resulting state of both aetiological developments will, in its consequences, be identical, i.e. the emergence of temporal lobe or limbic seizure-like activity with very similar clinical manifestations. In this context it is worth noticing that there is a high correlation between the two questionnaires developed for the detection of the seizure-like symptoms, i.e. the CPSI and LSCL–33 (Spearman R 0.75, N=100, $p<0.0001$; our unpublished results).

Another interesting result of the study concerns the difference between smokers and non-smokers in the CPSI score. This finding is in accordance with the evidence of a more frequent occurrence of stressful life experiences such as physical, sexual and/or verbal abuse in childhood, family dysfunction, and parental divorce in smokers [5, 6, 7, 8, 9, 10] and the evidence that this experience could start the development of temporolimbic dysfunction [4]. In cigarette dependence, the role of stress with its negative emotions is widely recognised. The symptoms of distress can act as triggers evoking strong urges to use tobacco and to motivate for smoking across all its stages such as initiation and experimentation, maintenance, and relapse [7,20,21,22,9,10,23]. The association between the higher frequency of seizure-like symptoms and the regular finding of heightened occurrence of distress symptoms in smokers [5,6,7,8,9] thus suggests another possible connection between stress and smoking. It is possible that in some smokers the heightened seizure-like activity could, through its association with psychopathological symptoms, represent a crucial aetiological factor for smoking. Symptom management is an important part of nicotine dependence treatment and prevention of relapse. In the context of the presented aetiological considerations and the results obtained in this study, the question about the enlargement of smoking cessation interventions by an anticonvulsant treatment in this specific subpopulation of smokers is fully justified.

ACKNOWLEDGEMENTS

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MANUAL DEXTERITY OF OLDER ADULTS LIVING IN HOMES FOR ELDERLY PEOPLE

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ABSTRACT

Aging affects functions of the hands among older adults living in homes for elderly people. The lack of opportunities to be active in daily living tasks during the day leads to the impairment of hand functions, upper extremity functions, grip functions, and overall manual dexterity. The aim of our experiment was to determine the impact of a six-month movement intervention programme on the hand function. We assessed the manual dexterity of older adults by means of the Test of Manipulation Functions, using the "Ministav" construction set. The sample tested was a group of 20 women and men, aged 70–93, who live permanently in a home for elderly people in Brno. The results represent the positive impact of the intervention programme on the hand function. The statistics proved a significant improvement in 7 subtests; only the subtest assessing the ability to lift the House object into a required height by the non-dominant hand using a finger grip proved deterioration. Generally, we succeeded in improving the co-ordination and co-operation of the upper extremities in most seniors; the quality of both the bidigital grip and the palm grip improved. The control measurements proved positive changes in targeted movements, the rapidity of the manual task performance increased, and the quality of cognitive functions improved.

ABBREVIATIONS USED

TMF – test of manipulation functions

INTRODUCTION

The hand function, the hand as a work tool, and the human manual dexterity have been the research objects of specialists in many, not only medicinal fields. Undoubtedly, they are important in geriatrics too, since the changes related to old age and aging have an important influence on the hand function. Significant changes or gradual deterioration of manual dexterity occur in seniors living in homes for elderly people

or other similar institutions providing full-time care to people in this age category.

The change of hand function caused by aging can be influenced by many factors – genetic, endocrine, and metabolic. Furthermore, it can be affected by diseases such as osteoarthritis, rheumatoid arthritis, osteoporosis; by pathological changes occurring both in soft tissues in muscles, tendons and blood vessels, and in bones, cartilages, and finger nails. Manual dexterity in old age is also affected by the environment, physical activities, food, and traumatic injuries during a person's life (1, 2).

For the aging population, living both independently and in institutions for elderly people, a good hand function, upper extremity function, and overall manual dexterity are means of ensuring their independence in basic daily activities (1, 2). Therefore, the preserved function of hands and upper extremities is a significant factor for seniors, since the possibility of looking after oneself and being independent of the others' help affects the overall life quality. Based on the results of their measurements, Falconer et al. (1991) support the hypothesis that the functional state of the hand correlates with the rate of independence in old age in people above 60 years of age. They conducted measurements with several groups of seniors with different life styles.

Deteriorated joint mobility is stated as the primary cause of the impaired hand function. Limited mobility further causes reduction of muscle strength, which leads to a negative influence on the grip function and the overall manual dexterity of the hand (3, 4).

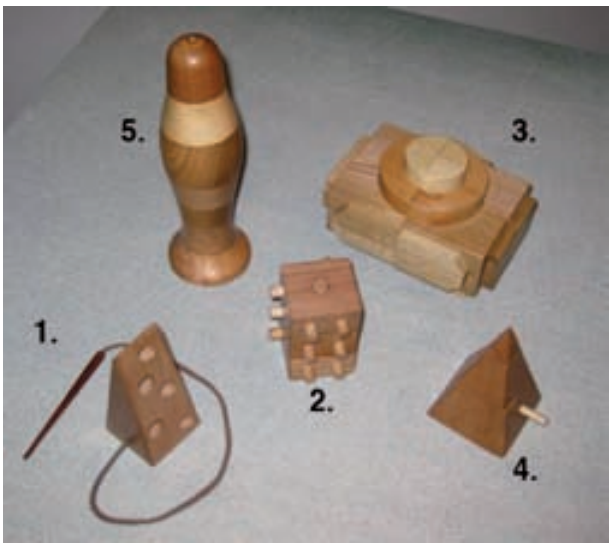


Figure 1
The Ministav construction set
Legend: 1. Needle, 2. Cube, 3. House, 4. Pyramid, 5. Mummy

Hughes et al. (1995) confirm in their study that reduced muscle strength, measured by the maximum grasp strength, is a significant risk factor that deteriorates the manual dexterity of the hand. Thus, besides other involutional changes, the aging process is accompanied by changes in muscles, with no significant difference between the sexes. Muscle strength measured by the maximum grasp strength and in pinch grip decreases with age, and according to subsidiary results men demonstrate greater strength than women in all age categories measured [5].

Buchman et al. (2005) compared the efficiency of upper extremities in a group of women and men of 65 and above, in relation to age. Men were stronger and had a bigger muscle mass. Women scored higher in the Purdue Pegboard test, while men were quicker in tapping with the index finger for 10 seconds. According to the results of the study, the differences in strength between the sexes decrease with age, whereas the differences in rapidity are not affected by age.

The everyday independent performance of daily life activities includes movements of the whole upper extremities, and as Carmeli et al. (2003) state, manual dexterity is thus practiced regularly. In this way, individuals sustain their agility, mobility and strength, and they practice the grip function of the hands and co-ordination of the extremities. Examples of performance and training of manual dexterity in daily living activities can be tying up shoe laces, fastening buttons, manipulation with a pen or cutlery, opening a bottle, or application of prescribed medicines.

In the Czech Republic, older adults living in homes for elderly people with all-day care have their meals made, medicines prepared, and all kinds of housework, such as cleaning, washing, ironing, clothes repairs, and shopping, provided. They also have all paper work and common formalities attended to. Thus, in this group of seniors training and using of hands is only limited to basic daily activities, like self-feeding, dressing, personal hygiene, and involvement of hands in moving from one place to another. The lack of opportunities to look after oneself, clean one's room, cook one's meals, or otherwise employ one's hands during the day leads to a deterioration of manual dexterity and grip function, and to a restriction of the functioning of upper extremities as a whole.

MATERIALS AND METHODS

The main goal of the study was to assess the impact of an intervention movement programme on manual dexterity in a group of seniors.

The group tested consisted of 20 adults living in a home for elderly people in Brno–4 men and 16 women 70–93 years old; the age average was 83.9 years. All subjects were right-handed and were selected randomly from within participants

Table 1
The results of changes due to the intervention programme in subtests of TMF using the Ministav construction set

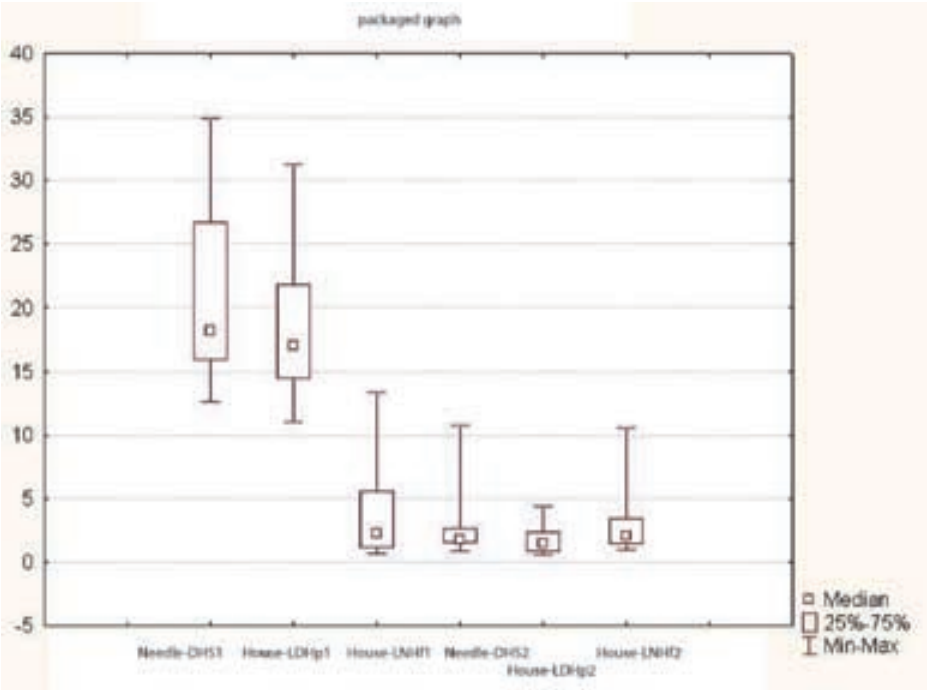
	1			2			
	mean	n	s	mean	n	s	*d*
Needle-BHS	17.43	20	5.009	17.37	20	8.062	0.01
Needle-DHS	20.8	20	6.864	18.18	20	4.909	0.43
Needle-NHS	26.65	20	9.875	24.74	20	15.74	0.14
Cube-BHD	2.779	20	1.079	3	20	2.77	–0.10
Cube-BHA	3.587	20	1.331	3.96	20	3.266	–0.15
Cube-DHD	2.37	20	0.444	2.641	20	1.574	–0.23
Cube-DHA	3.289	20	1.112	3.83	20	3.388	–0.21
Cube-NHD	2.801	20	0.769	3.746	20	3.518	–0.36
Cube-NHA	3.482	20	1.471	3.791	20	2.524	–0.15
Cube-AP	41.28	19	33.97	32.34	19	18.21	0.32
House-LDHp	3.848	18	3.596	2.383	19	2.135	0.49
House-LDHf	9.132	18	30.2	4.685	18	9.508	0.19
House-LNHp	3.786	18	3.833	3.003	18	2.887	0.23
House-LNHf	1.687	18	1.068	2.746	19	2.131	–0.61
House-AP	37.13	19	33.36	32.16	20	19.02	0.18
Pyramid-BHD	5.825	20	2.693	4.889	20	2.739	0.34
Pyramid-BHA	10.41	20	3.86	8.439	20	4.745	0.45
Pyramid-DHD	5.413	20	1.756	5.445	20	2.813	–0.01
Pyramid-DHA	11.02	19	4.896	7.954	20	3.742	0.69
Pyramid-NHD	5.042	20	1.547	5.464	20	2.561	–0.20
Pyramid-NDA	12.07	20	5.173	9.434	20	3.319	0.60
Mummy-DHD	10.22	20	2.525	10.24	20	5.701	0.00
Mummy-DHA	22.32	20	10.42	20.36	20	12.79	0.17
Mummy-NHD	11.17	20	2.385	11.7	20	7.535	–0.09
Mummy-NHA	26.58	20	15.07	21.33	20	10.33	0.40
Mummy-AP	55.23	19	28.65	42.96	20	17.86	0.51

Legend:
n – number of tested probands
s – standard deviation
d – Cohen's effect size coefficient
mean – average time needed to accomplish the subtest
1 – starting measurement
2 – control measurement

Needle – BHS – both hands sewing
Needle – DHS – dominant hand sewing
Needle – NHS – non-dominant hand sewing

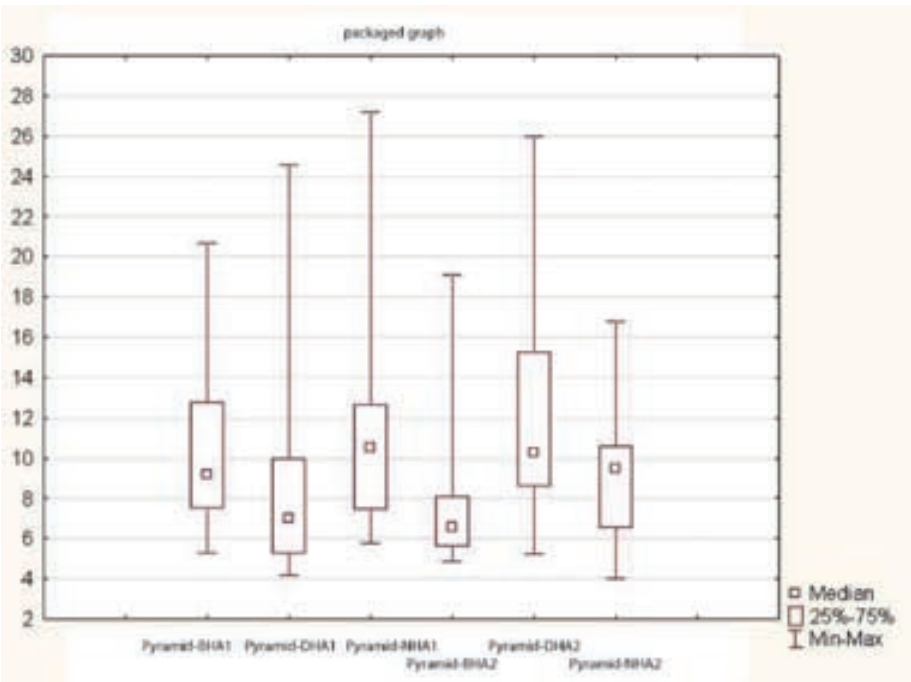
Cube – BHD – both hands dismantling
Cube – BHA – both hands assembling
Cube – DHD – dominant hand dismantling
Cube – DHA – dominant hand assembling
Cube – NHD – non-dominant hand dismantling
Cube – NHA – non-dominant hand assembling
Cube – AP – assembling the Cube according to pattern
House – LDHp – lifting the House by dominant hand using a palm grip
House – LDHf – lifting the House by dominant hand using a finger grip
House – LNHp – lifting the House by non-dominant hand using a palm grip
House – LNHf – lifting the House by non-dominant hand using a finger grip
House – AP – assembling the House according to pattern

Pyramid – BHD – both hands dismantling
Pyramid – BHA – both hands assembling
Pyramid – DHD – dominant hand dismantling
Pyramid – DHA – dominant hand assembling
Pyramid – NHD – non-dominant hand dismantling
Pyramid – NHA – non-dominant hand assembling
Mummy – DHD – dominant hand dismantling
Mummy – DHA – dominant hand assembling
Mummy – NHD – non-dominant hand dismantling
Mummy – NHA – non-dominant hand assembling
Mummy – AP – assembling the Mummy according to pattern



Legend:
Needle – DHS – dominant hand sewing
House – LDHp – lifting the House by dominant hand using a palm grip
House – LNHf – lifting the House by non-dominant hand using a finger grip

Diagram 1.
Depiction of the level of change of given parameters in the Needle and House objects.



Legend:
Pyramid – BHA – both hands assembling
Pyramid – DHA – dominant hand assembling
Pyramid – NHA – non-dominant hand assembling

Diagram 2.
Depiction of the level of change of given parameters in the Pyramid object.

Table 2.
The results of statistically significant changes due to the intervention programme in given subtests

Wilcoxon test	N	T	p	*d*	+/–
Needle-DHS1 & Needle-DHS2	20	29.0	0.004	0.43	score decrease
House-LDHp1 & House-LDHp2	18	41.0	0.052	0.49	score decrease
House-LNHf1 & House-LNHf2	18	35.0	0.027	–0.61	score increase
Pyramid-BHA1 & Pyramid-BHA2	20	30.0	0.005	0.45	score decrease
Pyramid-DHA1 & Pyramid-DHA2	19	4.0	0.000	0.69	score decrease
Pyramid-NHA1 & Pyramid-NHA2	20	13.0	0.000	0.60	score decrease
Mummy-NHA1 & Mummy-NHA2	20	46.0	0.027	0.40	score decrease
Mummy-AP1 & Mummy-AP2	19	42.0	0.032	0.51	score decrease

Legend:
N – number of tested probands
T – value of the tested criterion
p – minimum level of statistical significance in which zero hypothesis is rejected
d – Cohen's effect size coefficient
+/– – score increase/decrease

of a one-year-long research programme, which is being carried out currently in the institution. Manual dexterity was one of the several tested attributes of the overall functional efficiency of seniors.

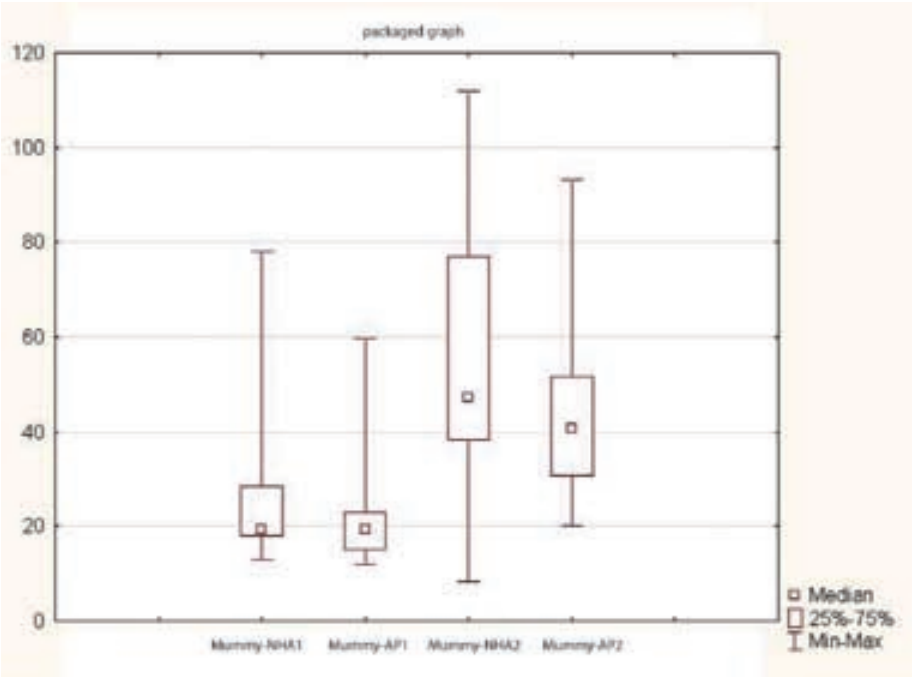
The movement intervention programme was conducted twice a week in the gymnasium of the home for elderly people. A complete exercise unit was 50 minutes long, out of which approximately 10 minutes (thus 20 minutes a week) were focused on sustaining and improving motor activity of fingers, co-ordination and hand grip function. For the training of hands and fingers we used rubber balls, wooden rods, balls with spines, overballs, Thera-bands, plastic cups of various sizes, and paper.

To evaluate hand dexterity in the group the Test of Manipulation Functions (TMF) was used, using the Ministav construction set. According to J. Vyskotová, the author of the test (2007), the Ministav set not only serves as a means to test manual dexterity and hand grip function, but is also used to diagnose and treat hand manipulation malfunctions. The Ministav construction set comprises 5 wooden objects: Needle, Cube, House, Pyramid, and Mummy (*Fig. 1*). Each object may be manipulated, assembled and dismantled in a different way. During manipulation their various shapes allow the use of many grip types and the persons tested also practice their attention, cognitive functions, and memory. Since manipulation with the objects involves both upper extremities all the time, their co-ordination is also strengthened. The complete TMF comprises 26 subtests. For each task the time needed for its accomplishment is measured and the outcome score is the average of three trials.

The starting data were obtained before the start of the research at the beginning of 2009; a control measurement was carried out after 6 months of intervention, in July 2009. To process the results of the two measurements methods of mathematical statistics were used, and factually and statistically significant changes were recorded in Table 2. The changes that show improvement in the subtests recorded in Table 2 were then depicted in *box diagrams 1, 2, and 3*. To detect the differences between the first and second measurements the Wilcoxon *t*-test was used, because the Shapiro-Wilks Normality Test showed that the data do not come from normal distribution. To compare the ILS variables the non-parametric Wilcoxon t-test for paired samples was used. The level of factual significance and the level of statistical significance $\alpha = 0.1$ were determined at the beginning. In regard to the explorative character of the research we consider the determined level of statistical significance expedient. Using the Cohen's *d* effect size coefficient the level of the factual significance of the obtained variables was assessed. For $d > 0.8$ the effect is high, for *d* between 0.4–0.8 the effect is medium, and for $d < 0.2$ the effect is small [10].

RESULTS

As seen in *Table 1*, out of the 26 tested items of TMF, 15 showed improvement in the average time needed for the accomplishment of the task. However, statistically significant changes on the 10%-level of significance were only achieved in 8 subtests out of 26 (*Table 2*). Both statistically and factually significant improvement was achieved in 7 subtests, deterioration only in 1.



Legend:
Mummy – NHA – non-dominant hand assembling
Mummy – AP – assembling the Mummy according to pattern

Diagram 3
Depiction of the level of change of given parameters in the Mummy object

DISCUSSION

The results given above demonstrate a positive effect of the intervention movement programme on the manual dexterity of older adults living in a home for elderly people. The co-ordination and co-operation of upper extremities in manual activities were improved according to Vyskotová and Vaverka (2004), which is proved by the Needle test in bimanual sewing in all the 20 persons tested, by the House test in lifting the House using a palm grip in 18 persons, and by the Pyramid test in all assembling subtests. For most seniors assembling the Pyramid was easier than dismantling it. When dismantling the Pyramid most persons did not start with the correct procedure and the time delay is reflected in the outcome results. In the correct procedure the side peg, holding the whole object locked together, should be removed first, then the removal of the top of the Pyramid follows, and in the end the middle part is removed. Undoubtedly, the reduced sensitivity of the seniors' fingertips and the smooth surface of the top part of the Pyramid also made the object difficult for the seniors to grip, which again was reflected by higher time scores of dismantling.

The improvement of the quality of bidigital grip (using the thumb and index finger) and the positive effect on targeted movements are demonstrated by the Mummy test in non-dominant hand assembling, and by the Pyramid test in bimanual assembling and dominant and non-dominant hand assembling. In 18 seniors statistically as well as factually significant improvement occurred. The ability and quality of the palm grip was improved, in the House test in lifting by the dominant hand using palm grip. Significant improvement of the handgrip strength was proved in most seniors who participated in the whole one-year research programme. The handgrip strength was measured by a hand dynamometer, but the results have not been published in the context of this study.

On the contrary, weakening of finger grip occurred in 18 persons in the House test in lifting by the non-dominant hand using finger grip. To lift all four parts of the House object by 20 cm proved difficult for most seniors. Accomplishment of this subtest requires the exertion of a sufficient finger grip strength and co-ordination of the thumb and the other fingers, not only to lift the object but also to keep its four parts together.

In addition, participation in the intervention movement programme positively affected the quality of cognitive functions of the tested persons. The control results of the Mummy test in assembling according to pattern show statistically and

factually significant improvement, which is demonstrated by a medium improvement effect (Cohen's coefficient $d = 0.5$). On the other hand, improved values of the control results of the Cube and House tests in assembling according to pattern cannot be regarded as statistically or factually significant.

The starting results showed that manipulation with the Cube object was the easiest for all the 20 persons tested. Although the time results in January 2009 were among the quickest, only minimum changes (deterioration) occurred in the control tests for this object. However, this change did not reach the level of statistical significance and therefore the Cube test is not included in Table 2.

The possibility of influencing positively the hand function by regular movement intervention is also reported by Ranganathan et al. (2001). The results of their measurements indicate that after an eight-week regular training improvement occurred in the rapidity and accuracy of finger movements, in the strength of pinch grip, and in the measured excitability of motor neurons in hand muscles in the control group. However, their intervention programme focused exclusively on the function of the hand and upper extremities.

Our regular movement programme also positively affected the manual dexterity and hand function of older adults living in a home for elderly people. The fact that the intervention programme focusing on manual dexterity of seniors was only carried out for 20 minutes a week must be considered as a possible cause why the positive changes demonstrated by the control results as seen above were not more significant. However, the intervention movement programme focused on the overall functional efficiency of the seniors, not only on the training of finger motor activity and the practice of grip and manipulation hand functions.

So far, the results of this study could not be compared to other data on an equivalent group of persons, since no other results of evaluation of manual dexterity by TMF using the Ministav construction set have been published.

CONCLUSION

Manual hand dexterity of older adults living in homes for elderly people can be improved, sustained, and trained by regular exercise. In most seniors the manipulation hand function was positively affected. Statistically processed results of the Test of Manipulation Functions indicate the improved quality of bidigital grip, using the thumb and index finger. The quality of palm grip, co-ordination and co-operation of hands during the activities have also improved. In addition, by the intervention movement programme an improvement of targeted movements, rapidity of the manual task performance, and the quality of cognitive functions was achieved. Statistically and factually significant deterioration was recorded in only one test, lifting the House object by the non-dominant hand using finger grip.

Sufficient opportunities to employ both upper extremities and hands during the day certainly contribute to the state of manual dexterity. The sustained function of the hands and whole upper extremities enables seniors in homes for elderly people to be independent and self-reliant in common activities of daily life.

Training of independence and self-reliance should therefore be an integral part of the care provided to seniors living in social institutions. The level of self-reliance, the ability to look after oneself, and the manual dexterity are closely interrelated. Their interrelation is a stimulus for our future research in the reported group of seniors.

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ASSESSMENT OF THE LEFT VENTRICLE DIASTOLIC FUNCTION IN A GROUP OF PATIENTS WITH CHRONIC ISCHAEMIC HEART DISEASE AND REGULAR PHYSICAL ACTIVITY

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ABSTRACT

Aim

Assessment of the left ventricle diastolic function in a group of patients with stable coronary artery disease and regular physical training.

Methods

The study included thirty patients with stable coronary artery disease. Every patient had participated in the conducted 3-moth physical training in Department of Functional Diagnostic and Rehabilitation St. Anna Hospital. After one year the patients were retrospectively divided into two cohorts according to their physical activity. The patients in cohort C (consisting of 14 patients) continued in aerobic physical training after the end of the rehabilitation programme. The patients in cohort N (consisting of 16 patients) had stopped their training after finishing the conducted programme in St. Anne's Faculty Hospital.

The peak diastolic velocities of myocardial motion were measured at individual LV walls: septum, lateral, anterior, and inferior walls. In addition, to determine global LV diastolic function, the four-site mean diastolic velocity was calculated (Ea glob, Ea/Aa glob). The velocities were evaluated at rest and at the maximal load.

According to blood supply, left ventricular walls were divided into five groups: 0 – walls supplied by non-stenotic artery; 1 – walls supplied by artery with coronary stenosis ≤ 50 %; 2 – walls supplied by artery with stenosis 51–70 %; 3 – walls with stenosis of supplying artery 71–99 %; 4 – walls with totally occluded supplying artery. For every patient the difference between the values Ea and Ea/Aa for each wall at the end of the study and the values at the beginning of the study was assessed. The values of the particular walls were divided into

Table 1
Population under study

	Cohort C	cohort N	
Age (years)	60±10	69±8	*
Number of arteries with stenosis ≥ 70 %	1.6±1.1	1.8±1.2	
DM	43 %	19 %	
MI	50 %	63 %	
Hypertension	100 %	100 %	
HLPP	100 %	94 %	
EF (%)	50.8±10.8	48.6±12.4	
Male/female	13/1	9/7	*

Explanatory notes: values are shown as average ± standard deviation; EF: LV ejection fraction; MI: myocardial infarction; DM: diabetes mellitus; HLPP: hyperlipoproteinaemia; * p<0.05 between cohorts

Table 2
Changes of the value characteristics of diastolic function

	rest						stress					
	Ea			Ea/Aa			Ea			Ea/Aa		
Cohort	C	N		C	N		C	N		C	N	
0	–0.64±2.08	–1.44±1.66		–0.02±0.14	–0.10±0.24		–0.44±2.53	–1.03±2,24		–0.14±0.25	0.04±0.27	
1	0.27±2.93	–0.26±1.37		–0.05±0.28	0.03±0.12		1.25±2.78	2.05±3.37		0.01±0,17	0.11±0.20	
2	0.59±2.62	–1.64±3.69		0.13±0.08	–0.11±0.38		0.51±2.87	0.62±4.97		0.00±0.20	0.13±0.43	
3	0.55±3.68	–0.66±1.71		0.03±0.34	0.14±0.30		–0.04±4.86	–0.48±3.00		0.09±0.57	0.25±0.57	
4	–0.48±2.77	–0.77±2.28		–0.06±0.22	0.03±0.18		**4.24±3.65**	**–0.68±2.74**	*	**0.29±0.39**	**–0.03±0.24**	*
Global function	**0.05±2.94**	**–0.89±2.01**	*	–0.02±0.26	0.02±0.26		**1.27±3.75**	**–0.13±3.20**	*	0.06±0.36	0.09±0.38	

Explanatory notes: values are shown as average ± standard deviation;* p<0.05 between cohorts; rest = investigation at rest; stress = investigation during maximal load; C = cohort C; N = cohort N; groups 0,1,2,3,4 = according to blood supply; global function = Ea global or Ea/Aa global as the average of all LV walls

5 groups according to blood supply (these 5 groups were created using coronarography).
The differences of these values at rest and stress between both cohorts of patients were statistically processed using an unpaired t-test; p<0.05 was considered statistically significant.
Results: In global diastolic function, the values of Ea global in cohort C were improved by 0.05±2.94 cm/s at rest, and by 1.27±3.75 cm/s at maximal load, while the values of Ea global in cohort N were diminished by –0.89±2.01 cm/s (p<0.05 versus cohort C), and by –0.13±3.20 cm/s; (p<0.05 versus cohort C) at maximal load.
The most important benefit with diastolic function was found in group 4 (groups with totally occluded coronary artery). The values of Ea in cohort C were improved by 4.24±3.65 cm/s, while the values in cohort N were diminished by –0.68±2.74 cm/s; (p<0.05 versus cohort C) at maximal load.

Results

The results of the other Ea values were not significant.

The Ea/Aa values in group 4 in cohort C were improved by 0.29±0.39 cm/s at maximal load, while the values of Ea/Aa in cohort N were diminished by –0.03±0.24 cm/s; ($p<0.05$ versus cohort C) at maximal load. The results of the other Ea/Aa values were not significant.

Conclusion

Our patients with 12 months' training improved their global diastolic function. The most important benefit was found in walls supplied by occluded artery.

ABBREVIATIONS USED

TDI – tissue Doppler imaging
LV – left ventricle
Sa – systolic phase of cardiac cycle
Sa´– peak of isovolumic contraction
Ea – fast filling diastolic phase
Aa – atrium contraction end of diastolic phase
EF LV–LV ejection fraction
MI – myocardial infarction
DM – diabetes mellitus

INTRODUCTION

The effects of regular physical activity on the cardiovascular system and myocardial function are global. The risk factors are reduced (by changing the way of life, strength of thews). Heart rate and blood pressure are decreased, the peripheral venous tone is improved, and a positive influence on the left ventricle (LV) is probable.

Tissue Doppler imaging (TDI) is an echocardiographic method using the Doppler effect. Using this method it is possible to measure the velocity of myocardial motion in both systolic and diastolic phases of cardiac cycle [1]. The difference between the classic Doppler sonography and TDI is in using special filters that eliminate signals which are repulsed back by blood cells, and reversibly intensify signals that are repulsed by the myocardium (these signals are marked with high amplitude and low frequency).

There are two types of TDI: pulsed TDI and colour TDI. Using the pulsed TDI we get the characteristic curve, which consists of three main waves *(Figure 1)*. The positive Sa wave represents the systolic phase of the cardiac cycle. This wave is frequently two-phased with a first slim peak of isovolumic contraction (Sa´) and a second, wider wave of LV ejection. The first negative wave after the Sa wave is called Ea; it represents fast filling of the ventricle in the diastolic phase of the cardiac cycle. The second negative wave (Aa) grows from atrial contraction at the end of the diastolic phase of the cardiac

Figure 1. Characteristic curve of pulsed TDI.

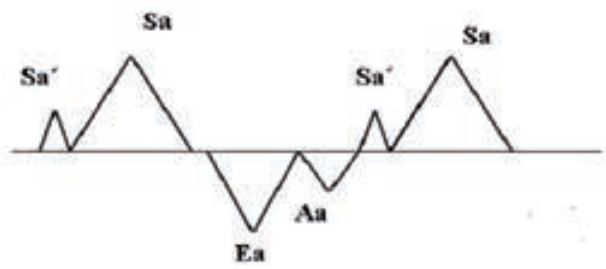

Figure 1
The characteristic curve of pulse TDI
Sa – systolic phase of cardiac cycle
Sa´-peak of isovolumic contraction
Ea – fast filling diastolic phase
Aa – atrium contraction end of diastolic phase

cycle. The Aa wave is missing in the case of atrial fibrillation [2]. During exercise tests the waves Ea and Aa are often fusing [3] caused to the faster heart rate.

By measuring the amplitude of these single waves, the maximal velocity of each myocardial segment during the cardiac cycle can be evaluated. In myocardial pathologies the velocity values for each segment and also the overall value of the ventricle function are changed. The velocity of all 17 myocardial segments can be measured [4]. Physiologically, the velocities are getting higher in segments from the apex toward the heart base. TDI can be used for the evaluation of both regional and global function of both ventricles (both systolic and diastolic ventricle function). We can prove myocardial ischaemia, and reversible and non-reversible myocardial dysfunction [2]. During ischaemia the maximal Sa and Ea velocities are reduced. The change of Aa is not significant, so the Ea/Aa ratio in the ischaemic area is getting down [1].

The purpose of this study was to assess the effect of aerobic training on the left ventricular diastolic function in a group of patients with chronic ischaemic heart disease.

MATERIALS AND METHODS

The study included thirty patients with stable coronary artery disease. These patients were retrospectively divided into two cohorts with different regular physical training. The cohort C consisted of 14 patients. These patients had participated in a conducted 3-month physical training at the Department of Functional Diagnostics and Rehabilitation of St. Annes' Faculty Hospital, and after the 3 months they continued with individual training for 9 more months. The regular physical training consisted of 3 phases in 60 minutes 3 times a week. The

first phase of the training is called warming-up and lasts for ten minutes. The second phase is an aerobic period and lasts for 35 minutes. This phase consists of power training and riding a bicycle ergometer. The third phase is a relaxation phase and lasts for 15 minutes. The 9-month individual training consists of regular physical activity performed for one hour at least three times a week. As a regular physical activity the patients chose one of the following sports: riding a bicycle ergometer, cycling, or swimming. The cohort N consisted of 16 patients. These patients stopped the training after having finished with the conducted programme. The cohort's characteristics are shown in *Table 1*.

At the beginning of the study coronarography was performed. According to blood supply, the left ventricular walls were divided into five groups: 0 – walls supplied by non-stenotic artery; 1 – walls supplied by artery with coronary stenosis ≤ 50 %; 2 – walls supplied by artery with stenosis 51–70 %; 3 – walls with stenosis of supplying artery 71–99 %; 4 – walls with totally occluded supplying artery.

Rest and stress dobutamine/atropine echocardiography was performed in all patients before the training programme and one year later. Three days before the rest/stress dobutamine echocardiography the beta blockers were discontinued. Using the commercially available equipment Sonos 5500 (Hewlett-Packard, US) with a 2.5 MHz transducer, echocardiography was performed in standard views – parasternal long axis, parasternal short axis (level of papillary muscles), apical 4- and 2-chamber views. The peak diastolic velocities of myocardial motion were measured at individual LV walls: septum, lateral, anterior, and inferior walls. In addition, to determine the global LV diastolic function, the four-site average diastolic velocity was calculated (Ea glob, Ea/Aa glob). The velocities were evaluated at rest and at the maximal load.

For every patient the difference between the values Ea, Ea/Aa for each wall at the end of the study and the values at the beginning of the study was assessed. The values of the particular walls were divided into 5 groups according to blood supply (these 5 groups were created using coronarography). The differences of these values during rest and maximal stress between both cohorts of patients were statistically processed using an unpaired t-test, $p<0.05$ was considered statistically significant.

RESULTS

The results are shown in *Table 2*.

In the global diastolic function, the values of Ea global in cohort C were improved by 0.05±2.94 cm/s at rest, and by 1.27±3.75 cm/s at maximal load, while the values of Ea global in cohort N were diminished by –0.89±2.01 cm/s ($p<0.05$ versus cohort C), and by –0.13±3.20 cm/s; ($p<0.05$ versus cohort C) at maximal load.

The most important benefit to the diastolic function was found in group 4 (groups with totally occluded coronary artery). The values of Ea in cohort C were improved by 4.24±3.65 cm/s, while the values in cohort N were diminished by –0.68±2.74 cm/s; ($p<0.05$ versus cohort C) at maximal load.

The results of the Ea values from other walls were not significant.

The Ea/Aa values in group 4 in cohort C were improved by 0.29±0.39 cm/s at maximal load, while the values of Ea/Aa in cohort N were diminished by –0.03±0.24 cm/s; ($p<0.05$ versus cohort C) at maximal load.

The changes of the results of the other Ea/Aa values were not significant.

In cohort C, as the stress test was performed, 12 of 14 patients had a stress-induced kinetic disorder (2 patients had negative stress tests). In cohort N, as the stress test was performed, 12 of 16 patients had a stress-induced kinetic disorder (4 patients had negative stress tests, but 2 of them had the typical stress-performed chest pain without objective kinetic disorders).

DISCUSSION

In our work we used TDI to assess changes of the LV diastolic function. In patients with chronic ischaemic heart disease we performed the maximal stress test.

The regular physical activity has a positive influence on the diastolic function of the left ventricle. In our study we found an improvement of the global diastolic function during the rest and also during the maximal load. However, our results are not the same as the results in the Yu CM study [5], which proved no progression of diastolic dysfunction in a group of physically active patients.

We have to be cautious in our conclusion of diastolic function improvement, because the age average in both cohorts is not the same. The diastolic function is known to worsen over the age [6], and the patients in cohort N were significantly older than those in cohort C. And there was also a difference between the substitution of men and women in both cohorts. Nowadays the influence of regular physical training on the progression of age-caused diastolic dysfunction is not clear. Some studies proved the influence of regular physical training [7]; similarly in the study of Arbab-Zadeh et al. [8], in which sedentary seniors versus master athletes were compared. The conclusion drawn there was that prolonged endurance training preserves ventricular compliance with aging and may help to prevent heart failure in the elderly.

However, the results of some studies are different; thus, in the study of Nottin et al. [9], in which master athletes with long-

term endurance training were compared with sedentary seniors and young adult men. The authors concluded that endurance training does not prevent from the LV diastolic dysfunction.

STUDY LIMITATIONS

Our study has several limitations. The interpretations of the results may be limited by a relatively small number of patients in both cohorts. Also, our study can be influenced by the difference between the number of men and women and the difference between the patients' age in both cohorts.

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ROSACEA FULMINANS

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KEY WORDS

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ABSTRACT

Rosacea fulminans is interpreted as the maximum variant of rosacea. This illness typically appears suddenly on the mid-face of young women. It is a severe eruption of pustules, monstrous coalescent nodules, and cystic swellings. Multifactorial aetiology has been suggested. The disease requires special care, mostly treatment with oral corticosteroids and isotretinoin is necessary. A case of rosacea fulminans is presented. In a 20-year-old woman with no previous history of acne or rosacea there suddenly developed erythema and oedema, fluctuant nodules, pustules and confluent draining sinuses, only the face was affected. The standard therapeutic combination of systemic steroids and retinoids had a positive effect. No side effects of the therapy were present, almost complete healing was reached. The patient is still in the follow-up though the troubles should not recur.

INTRODUCTION

Rosacea fulminans is interpreted as the maximum variant of rosacea. This disease typically appears suddenly on the mid-face of young women. A lady of the age of twenty with the above-mentioned diagnosis is presented. Rosacea fulminans is described in detail with a view to the latest literature. Special aspects of our case are underlined.

CASE REPORT

A 20-year-old woman was referred to our Acne Clinic by a practical dermatovenereologist because of severe facial eruption. The patient's troubles started suddenly five weeks ago. A marked erythema with many nodules and pustules was present. She had been diagnosed with acne vulgaris and managed first by local therapy (benzoyl peroxide and clindamycin in gel), later (ten days before consultation at our department) peroral antibiotics therapy with doxycycline 100mg daily was started. However, the troubles did not improve.

At the first consultation in our Acne Clinic, the patient presented with a marked erythema and oedema, fluctuant

Figures 1–2
The patient before steroid and isotretinoin treatment

Figures 3–4
The patient after 10 days of steroid treatment

nodules, pustules, and confluent draining sinuses affecting only the face (chin, cheeks and forehead) [Figs. 1–2]. Only several comedones were detectable. A significant discomfort because of the unsightly appearance and pains of the lesions were the main troubles of our patient. Otherwise she was well, with no involvement of the trunk and limbs, without fever or musculoskeletal pains. Prior to the age of 20 years, she had no history of acne, rosacea or other skin diseases. In personal history phlebothrombosis of the left lower extremity two years before was important. The other history was not remarkable. Blood investigation was within normal limits except for slightly elevated CRP (8.3 mg/l). The culture of pustules was sterile. Biopsy was not performed.

The diagnosis of rosacea fulminans was established. The standard therapeutic combination of a systemic retinoid with a steroid was chosen. First, prednisone at a dose of 20mg daily was administered. Doxycycline 100 mg (later 50 mg) daily was continued for the next three weeks and then stopped. No local therapy was recommended. There was a rapid therapeutic response with significant improvement within a few days. The swelling disappeared, the nodules were reduced, the pains minimised [Figs. 3–4]. The steroid dose was reduced by 5 mg every week from the second week of its therapy. Four weeks later (one week after finishing doxycycline treatment), isotretinoin therapy was started at a dose of 0.5 mg/kg/day. Informed consent was signed. As peroral contraception was contraindicated, its other forms were recommended. At baseline, the laboratory tests were without normal limits (CRP decreased to 3.0 mg/l) except for leukocytosis (17.2 10^9/l, caused by corticosteroid treatment). On the face, erythema, papules, small pustules, and scars were present [Figs. 5–6]. Follow-up consultations were carried out at monthly intervals until finishing the isotretinoin treatment. No side effects except for slight cheilitis were present. Steroid treatment was finished after the first month of isotretinoin treatment (in total, 2 months of therapy), retinoid was given up to a total dose of 150 mg (for 10 months). At the end of isotretinoin treatment only small redness and slight scars on the cheeks were present [Figs 7–8]. The patient was very satisfied with her appearance. She was informed about the subsequent protection measures and is still in the follow-up.

DISCUSSION

Rosacea fulminans was first described by O'Leary and Kierland under the designation pyoderma faciale. It has been a matter of controversy ever since. One can say with certainty that it is not a variant of acne; neither is it pyoderma [1]. The name rosacea fulminans was coined by analogy with its acne counterpart, acne fulminans [2,3]. It is interpreted as the maximum variant of rosacea. This illness typically appears suddenly on the midface of young women [4]. Curiously, with some exceptions [7], it does not occur in males [1]. It is a sudden severe eruption of pustules and cystic swellings. Monstrous coalescent nodules and confluent draining sinuses occupy most of the face. Marked erythema and oedema are usually present. Comedones are usually absent or inconspicuous, as are other features of acne vulgaris or rosacea [1,3,5]. Seborrhoea is a constant feature but may be overlooked [1]. The main locations are the chin, cheeks and forehead [1,3,4,6], sometimes also the nose [3,6,7] and temples [3]. Localised forms may be confined to cheeks, jaw line or chin [6]. Previous acne or rosacea is usually denied; however, some authors perceive a connection to rosacea because, after a stormy blow-up, signs of rosacea often make their appearance. Some patients, too, have been flushers and blushers [1]. A culture of purulent discharge may be sterile or may yield a growth of commensal organisms including Staphylococcus epidermidis and Propionibacterium acnes. No laboratory abnormalities are found [3]. In histopathology, abscesses with pseudoepitheliomatous hyperplasia, widespread necrosis, and lakes of granulocytes are characteristic [1,8]. Scarring is mostly minimal [1], significant scarring can develop in severe cases [6]. The cause of the illness remains obscure. Multifactorial aetiology has been suggested following the demonstration of vascular changes, cell-mediated and humoral immune response, and increased density of Demodex mites in affected patients [9,10]. Often blamed is severe emotional stress, but some patients are stress-free [1]. Some cases have developed during pregnancy [3,5,11,12,13] or in females taking oral contraceptive pills [5], suggesting that hormonal factors may be a trigger. BsmI polymorphism of the vitamin D receptor gene in patients with rosacea fulminans is discussed [14]. Case reports suggesting thyroid and liver diseases [3,5], inflammatory bowel diseases [15,16], high-dose vitamin B supplements [17] or drug intake [3,18] as triggers were reported. The main differential diagnosis includes acne conglobata and acne fulminans. Androgen-producing tumours, bromoderma and iododerma must be also excluded, but tend to have a slower onset [1,4]. Rosacea fulminans requires special care. Treatment starts with oral corticosteroids (e.g. prednisolone 1.0 mg/kg per day) for one week to cool down the fire. Then oral isotretinoin is added, at around 0.2–0.5 mg/kg, rarely 1.0 mg/kg per day, with a slow tapering of the corticosteroid over the next two to three weeks. Isotretinoin is further continued until all inflammatory lesions dissapear (usually for three to four months) [2,3]; now the scheme up to a total dose of about 150/mg is preferred [19]. Draining abscesses should not be incised. A potent corticosteroid cream (for the first two

Figures 5–6
The patient after 4 weeks of steroid, before starting isotretinoin treatment

Figures 7–8
The patient at the finishing isotretinoin treatment

weeks only) can be applied [2,3]. In some cases successful treatment with moderately potent topical corticosteroids combined with systemic isotretinoin [20], application of Vleminckx packs (containing sulphur, calcium polysulphide and calcium thiosulphate), UVB, benzoyl peroxide, systemic antibiotics [5], dapsone [7,19] or a combination of topical agents and a systemic steroid [21] was reported. The prognosis of rosacea fulminans is excellent. Once the disease has been brought under control it does not recur [1]. Scarring is mostly minimal [2,4], though significant scarring develops in severe cases [6].

Our case is a typical example of rosacea fulminans: in a young woman with no previous history of acne or rosacea there suddenly developed erythema and oedema, fluctuant nodules, pustules and confluent draining sinuses; nothing but the face (chin, cheeks and forehead) was affected. Only several comedones were detectable. No triggers of the disease were found. Blood investigation was within normal limits except for slightly elevated CRP, a culture of the pustules was sterile. Biopsy was not performed because of typical clinical features (it would be only more stressing for the patient). The standard therapeutic combination of a systemic retinoid with a steroid was chosen. The corticosteroid was administered in a lower dose (only 0.3 mg/kg/day) and for a shorter time than is usual because of the history of phlebothrombosis. Antibiotics (given by a practical dermatologist) were retained until one month of usage because of their positive effect; they were finished one week before starting isotretinoin treatment as necessary (to avoid intracranial hypertension). Retinoid therapy was practiced according to all recommendations, only peroral contraception (contraindicated) was substituted with 2 other forms. No side effects of the therapy were present. A wonderful outcome was reached. The patient is still in the follow-up though the troubles should not recur.

CONCLUSIONS

A case of a young lady with the diagnosis of rosacea fulminans treated with peroral steroids and isotretinoin with a wonderful outcome is presented. Rosacea fulminans is a rare, but very distressing disease with possible scarring if not treated soon. All physicians should think about this diagnosis in patients with typical signs and should refer suspected cases to a dermatovenereologist so that effective treatment could be started in time. Once seen rosacea fulminans is never forgotten.

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LYMPHOGRANULOMA VENEREUM – A DIAGNOSTIC AND THERAPEUTIC DILEMMA?

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ABSTRACT

Lymphogranuloma venereum (LGV) is an infection caused by a subspecies of the bacterium *Chlamydia trachomatis* (invasive serovars L1, L2, or L3). It primarily causes painful swelling of the lymph nodes located closest to the site of initial infection. If untreated, the disease can progress and patients are needed in order to better consider the statements presented in this article. If untreated, it causes serious skin damages like scarring and genital elephantiasis. LGV is transmitted by direct sexual contact with genitals, rectum, or mouth. Once in the body, *Chlamydia Spp.* could reproduce themselves in the lymph nodes and could spread to other organs, provoking complications, such as the so-called pelvic inflammatory disease.

Both genital and extragenital manifestations of this disease are able to induce serious differential diagnostic difficulties, indirectly leading to progression and dissemination of the infection. The reason for that might be – not very rarely – related to non-typical clinical and histopathological findings.

This article presents two unusual cases of LGV with atypical histopathological/clinical findings and also focuses on alternative therapeutical approaches, such as surgical excision at stage 1, leading to positive outcome. However, the question if the surgical method could be used as a standard therapy at stage 1 remains open for discussion. It is not completely clear either if histopathological findings of LGV could reveal progress and/or changes through time as it happens in other diseases like pyoderma gangrenosum.

We conclude that both histological and clinical observation on a larger number of patients is needed in order to better consider the statements presented in this article.

INTRODUCTION

LGV, also known as lymphogranuloma inguinale, tropical bubo, Nicholas-Favre disease, and sixth venereal disease, is a sexually transmitted disease caused by the invasive serovars L1, L2, or L3 of the intracellular bacteria Chlamydia trachomatis [1].

In the United States LGV is generally considered to be a rare disease. According to the New York State Department of Health, the incidence of LGV is highest among sexually active people living in tropical or subtropical climates, including some areas of the southern U.S. [2]. Actually, this disease is endemic in East and West Africa, Southeast Asia, India, Caribbean basin, and South America, including Brazil. Indeed, a recent Brazilian study co-ordinated by proctologists points that, lately, LGV have been diagnosed in European countries, North America and Australia, mainly in men who have sex with men, and suggests the increasing incidence of LGV also in Brazil [3].

The most frequent clinical manifestation of LGV among men is a tender inguinal or femoral lymphadenopathy, which is in most cases unilateral [1]. Homosexually active men might have proctocolitis or inflammatory involvement of the perirectal lymphatic nodes [4].

The diagnosis is usually made serologically and by exclusion of other causes of inguinal lymphadenopathy or genital ulcers [1,2,5]. The differential diagnosis of LGV is often difficult, only after other causes of genital ulceration are ruled out. Even when LGV is suspected, investigations for other potentially co-existing sexually transmitted infections and some other tumorous lesions must be undertaken [2].

Positive diagnosis of LGV is difficult, requiring a combination of clinical experience and additional investigations [1,5]. LGV can be suspected on positive Chlamydia serology, isolation of *Chlamydia trachomatis* either from the infected site or histological identification of Chlamydia in the infected tissue (PCR, culture) [2,5]. Detection of nucleic acid (DNA) by amplification techniques (NAATs) such as the ligase chain reaction (LCR) or the polymerase chain reaction (PCR) are methods which are becoming established for routine testing of urethral, cervical, or urine specimens, but have rarely been used in the context of LGV, until the recent outbreaks in Western Europe. These methods are highly sensitive and specific and have now become widely available commercially, mostly in developed countries. Positive samples should be confirmed by real-time PCR for LGV specific DNA [1,2,5].

Another possibility is the *Chlamydia trachomatis* serology, which has been widely used. Three types of techniques have been used: the complement fixation (CF) test, the single L-type immunofluorescence test, and the micro-immunofluorescence test (micro-IF) – regarding the latter one as the most accurate serological assay. In general, a fourfold rise of antibody (both immunoglobulin M [IgM] and immunoglobulin G [IgG]) in the course of suspected illness is diagnostic of active infection.

Alternatively, single-point titres of >1/64 and >1/256 have been considered positive, since only an invasive infection like one caused by LGV could be responsible for such high titres. One of the main problems is that the test may lack sensitivity for the earlier manifestations of the disease – such as papules or ulcers (like in these two cases), and a high titre in the absence of symptoms cannot confirm LGV [1,5].

Culture on cycloheximide treated McCoy cells of material from LGV lesion is a very specific method, but its sensitivity is 75–85 % at best, and often closer to 30–50 % in the case of bubo aspirate [5]. This is in part due to the toxic effect of the pus on the culture cells and the method is labour intensive, expensive, and its availability is restricted. Its practical application to dermatological outpatient establishments is not always possible. The clinical pictures again play the leading role, as well as the serological finding and, if possible, PCR held in lesional skin or mucosa [5].

A 3-week course of antibiotics, usually tetracycline, doxycycline, or erythromycin is prescribed to eliminate the bacteria [5]. Buboes may remain after infection is cured and are usually surgically drained with a needle. Surgical repair of fistulas and erosion may be necessary in stage 3 of the disease [5]. In cases of elephantiasis, plastic surgery may also be helpful [5].

In this article, we focus on three major points: the unusual clinical presentation of the disease, simulating cutaneous tumours of variable localisation; a new histopathological presentation at the subacute stage of the disease in the form of fibrosing histiocytic macrophagocytic balanitis; suggesting a new surgical approach early in the primary stage of the disease.

CASE 1

History

A 36-year-old HIV-negative homosexual man complained of skin problems on the face and increased volume of cervical lymph nodes, dating from 3 weeks (Figs. 1a–1b). He had been in Libya for 3 months before cutaneous manifestations.

Clinical examination revealed an asymptomatic erythematous, erosive nodule of the right lower lip, approximately 12 mm in diameter, together with other two similar, smaller lesions located on the omolateral cheek and zygoma.

Histopathological findings

Ortho- and parahyperkeratosis on the epidermis, many neutrophil granulocytes, inflammatory infiltrates with plasmocytes, and some giant cells in the deeper dermis.

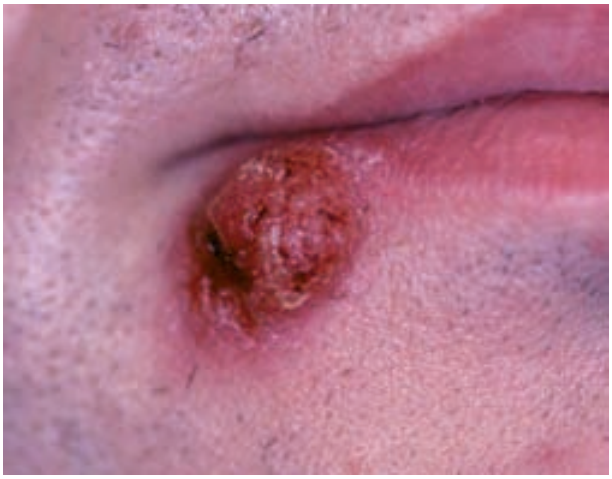

Figure 1a
Extragenitally localised papule, close to the right angle of the inferior lip (transitory mucosa), perilesional rubeosis.

Figure 1b
LGV – clinical manifestation (extragenital) in the area of the transitory mucosa.

Microabscesses could also be noted (Fig. 2).

Other complementary exams
Microbial culture of lesional tissue: negative for Gonococcus (Neisseria gonorrhoea). Microbial smear from the lesional tissue: negative for Staphylococcus aureus, Clostridium spp. Chlamydia smear from the urethra: negative.

Laboratory findings
- Leukocytosis of 15000/mm^3 before treatment. It was 6400/mm^3 after treatment.
- CRP (C-reactive protein) of 75. It was 8 after treatment.
- Erythrocyte sedimentation rate–60/78.
- PCR in lesional tissue: Chlamydia trachomatis-DNA-positive; Chlamydia pneumoniae-DNA-negative; Chlamydia psittaci-DNA-negative; Leishmania-DNA-negative.
- ELISA: Chlamydia-AK (autoantibodies) IgG (++) 6.77; IgA ++ (8.11) IgM ++ (4.36);
  HIV 1.2-AK: negative; TPHA negative, VDRL negative; hepatitis B/C antibodies negative.

Apparatus-based Diagnostics
Roentgenography (Rx): without pathologically findings.
Sonography-Abdomen: splenomegaly.
Sonography-Lymph nodes: multiple lymph nodes locoregionally and peripherally located lymph nodes (axillary).
CT – Computer tomography of the neck area: asymmetrical oropharynx structures at the area of the neck right, cervical lymph node involvement, asymmetrical subcutaneous tissue structures right in comparison to left. Massive infiltration of the dermis and subcutis.

Treatment and Outcome
Surgical excision of the affected lymph nodes, using local anaesthesia. Cervical lymph node excision resulted negative for metastatic tumour (Figs. 3a-b).
Treatment was initiated with Pentamidin (Pentacarinat®) 200 mg intramuscular (2x) plus oral Doxycycline 2x100 mg for three weeks, leading to complete remission.

CASE 2

An 82-year-old male, with a two-month history of a progressively indurating papule of the glans penis followed by ulceration. The initial clinical suspicion was of a skin tumour (Fig. 4).
His history was positive for internal diseases, including positive serology for rheumatoid arthritis, type 2 diabetes mellitus, glaucoma, heart failure (state after bypass intervention), and hypertension. The patient's systematic medication included: ISDN Isosorbitdinitrate 120 mg 1–0–0, Captopril 25/25 (1–0–1), Torasemid 10 mg 1–0–0, Kalinor (potassium chloride) 1–0–0, Methotrexate 10 mg 1–0–0.

Laboratory
- Erythrocyte sedimentation: 90/99, 76/88, 32/80.
- Ferritin: 1.225 (normal: 20–400 ng/ml).
- Transferrin : 1.52 (normal: 3–3.6 g/l).
- Haemoglobin 8,2 (normal: 8.7–11.2 mmol/l).
- Creatinine: 129 (normal: 53–133 µmol/l).
- Urea: 12.6 (normal:1.7–8.5 mmol/l).
- LDH: 4.1 (normal up to 3.75 mmol/l).

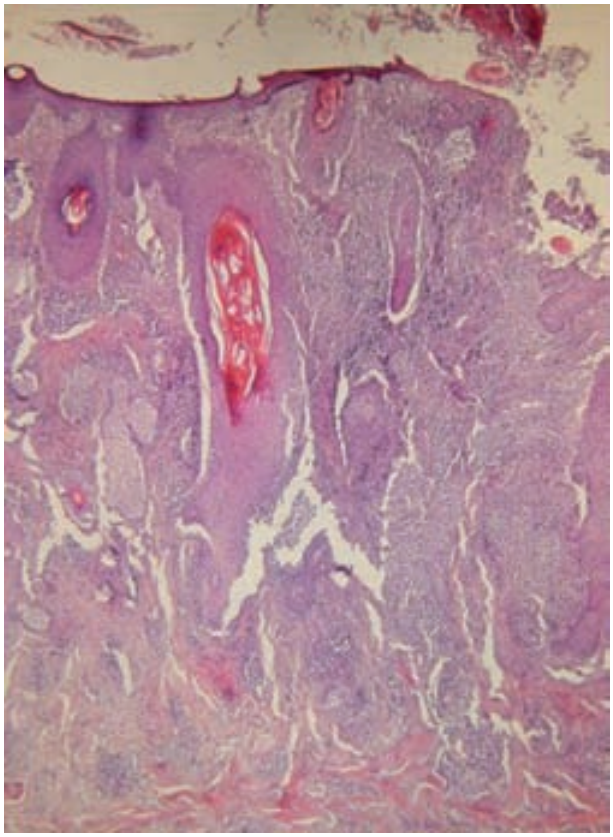

Figure 2
Histopathological finding after excision of the lesion: histology ortho- and parahyperkeratosis on the epidermis, many neutrophil granulocytes in the dermis, inflammatory infiltrates with plasmocytes and some giant cells in the deeper dermis, microabscesses.

- Immunofixation electrophoresis from the serum: paraproteinaemia type Kappa IgG could be observed.
- Immunofixation electrophoresis from the urine: no Bence Jones proteinuria.
- Serum protein electrophoresis: albumin- 54.5 (normal 60–71 %) / alpha 1–3.7 (normal 1.4–2.9 %) / gamma globulin -: 20.9 (normal 9–16 %).

Immunological parameters
- ANA: 1640 with a fine-speckled pattern.
- Autoantibodies against CCP: 8.2 (normal below 1).
- Rheumatoid factor: 92: (normal below 14 U/ml).
- pANCA, cANCA: negative.
- ENA: negative.
- Lymphocytic subpopulations: all data in normal issues.
- Quantitative immunoglobulins: IgG und IgA – normal, IgM –5.88 (norm 0.4–2.3 g/l).

Microbiology/Infections Serology
- TPHA test: negative.
- Chlamydia serology: IgA (ratio 1.47), IgM positive (ratio 1.08); IgG negative.
- Chlamydia smear lesional tissue of the penis: negative.
- VZV(Varicella zoster virus): IgG 3.4 (normal up to 1.1), IgM 1.3 (normal up to 1.1).
- Herpes simplex virus serology (HSV1, HSV 2): IgG positive–4.2, IgM negative.
- Fungi smear of penis: negative.
- Bacterial smear of penis: negative.

Apparatus-based diagnostics
- Roentgen thorax: right tuberculoma suspicious lesion.
- Ultrasonography lymph nodes and abdomen: steatosis of liver, left band: many up to 15mm big lymph nodes, confluent with each other, right band: some solitary painful lymph nodes.
- Roentgen of the lumbar area, sacral area, cervical area, pelvic floor, cranial: no osteolysis could be observed.

Histopathological findings
- Bone marrow biopsy: plasma cells and gammopathy with ambiguous significance.
- Histology: lymphocytic infiltrates with some eosinophil granulocytes (Fig. 5).
- Immunohistochemically: chronic macrophagocytic, histiocytic balanitis, fibrosing balanitis.
- DIF- direct immunofluorescence: negative.

Treatment and outcome
- Doxycycline 2x100 mg for 3 weeks and Octenisept® (antiseptic solution) 2–3 times a day were initiated, with complete remission (Fig 6) of skin lesions.

DISCUSSION

It is not impossible to think and conduct a patient as shown in cases Nos. 1 and 2 as skin cancer, because the clinical findings can be quite the same and the histopathology is often inconclusive [1,5]. One important step to differential diagnosis of an ulceration in the penis is to think about LGV [1,2,5]. A delay in the diagnosis increases the chance of complications and misunderstandings [5].
The fact that the initial stages of the disease can show a heterogeneous clinical picture, which would not always suggest to the clinician the idea of transmissible disease, is interesting.
Due to the history data (homosexuality and a recent time period spent in Libya, patient 1), the clinician receives important information and the differential diagnosis is amplified,

Figure 3a
Status after surgical incision of the inflectional papule. Good aesthetic results.

Figure 3b
Status of the operative cicatrices in the cervical area and the transitory mucosa after removal of threads.

without excluding any rare and untypical cutaneous manifestations of tropical and subtropical infections, such as LGV.
The enlarged lymphatic glands in the cervical area could be mistaken for locoregional metastases (Fig 1a, patient 1). The lesion in the infralabial area was removed ***in sano*** (completely) and the defect was closed by single skin stitches. Just in this case, extirpation of single lymphatic nodes from the submandibular area was applied, and the histological finding was identical. To exclude the planocellular carcinoma in the area of the transitive mucosae was of primary importance for the patient (Figs. 1c,1d). The histological finding provided surprising results: abscessed inflammation with neutrophils and, partially, granulomatous infiltrate (Fig. 2). The PCR in the lesional tissue confirmed an LGV–DNA (L1-L3) infection. The chlamydial serology was positive for IgM, as well as for IgG and IgA. Rare manifestations of cutaneous leishmaniasis were excluded by PCR methodology. The cause of the hepatosplenomegaly, discovered by ultrasonography, remained unclear. The patient's hepatic parameters were normal, so we exclude the possibility of any genesis induced by infection.
In spite of the good therapeutic results achieved by systematic medication, surgical excision of the whole lesion was also performed, leading quickly to full remission (stage 1a, patient 1). An excellent cosmetic effect was also achieved in the facial area (Figs. 3a, 3b).
LGV is evidently a disease which, within the so-called initial papule or stage 1a, can be surgically treated too. In case that an infection lymphadenopathy is supposed (confirmed by positive serology for IgM and/or PCR-DNA for Chlamydia trachomatis in the injured tissue), additional antibiotic therapy is also recommended [5].
Venereal lymphogranuloma is a disease which has a clear pathogenesis and its course develops by stages [1,5]. It is supposed that probably each stage has its respective clinical as well as histopathological morphology [5]. Frequently, in their clinical practice, dermatologists have to face serious diagnostic dilemmas, provoked by the non-specific clinical and, sometimes, histopathological findings in patients with LGV [1,2,5].
Genital ulcers may be present in sexually transmitted diseases besides LGV, such as syphilis, cancroid, genital herpes simplex, ulcerative herpes zoster, donovanosis; and in non-sexually transmitted disorders such as Behçet's syndrome, Crohn's disease, pemphigus vulgaris, erosive lichen planus, and others [1,2].
The ulcerative genital form of LGV presented by us is not characteristic of stage 1b, where the ulcerations are mainly located superficially, and without any fibrous coatings (Fig. 4a). The patient was hospitalised because of the clinical presence of a tumour in the stage of ulceration in the genital area. Such a manifestation in a patient aged 82 years (sexually inactive, according to the history of the disease) is not typical, either. Due to the positive serology for Chlamydia trachomatis, a systematic therapy by doxycycline was applied, leading to complete remission (Fig. 6). PCR for chlamydial DNA in the injured tissue was not held at the hospital.

Figure 4
Ulceration in the area of penis with fibrous coverings in an LGV patient.

The Kappa type paraproteinaemia found in the patient could lead to some disorders in the microcirculation at the periphery because of the sedimentation of paraproteins (combined with thrombocytes, erythrocytes, and fibrinogen in the vascular area) in the form of cryoglobulins and cryofibrinogen. However, in this case, the clinical remission would not be achieved by antibiotic therapy within 2–3 weeks, only if haemodilution or vasodilatation were applied. Indirectly, this diagnosis could not be confirmed.
The critically increased values of IgM serology do not eliminate the possibility of the presence of a localised, superinfected macerated genital form of varicella zoster viral infection. The non-specific histology eliminates the zoster diagnosis at the genital area and minimises the critical positive values of IgM with respect to VZV infection.
The positive serology with respect to *Chlamydia trachomatis* and the fast effect caused by the antibiotics indisputably make us think of a rare form of LGV infection.
The negative immunofluorescence of the injured tissue disproves the possibility of any immunologically initiated lesions within the framework of a seropositive, active rheumatoid arthritis.

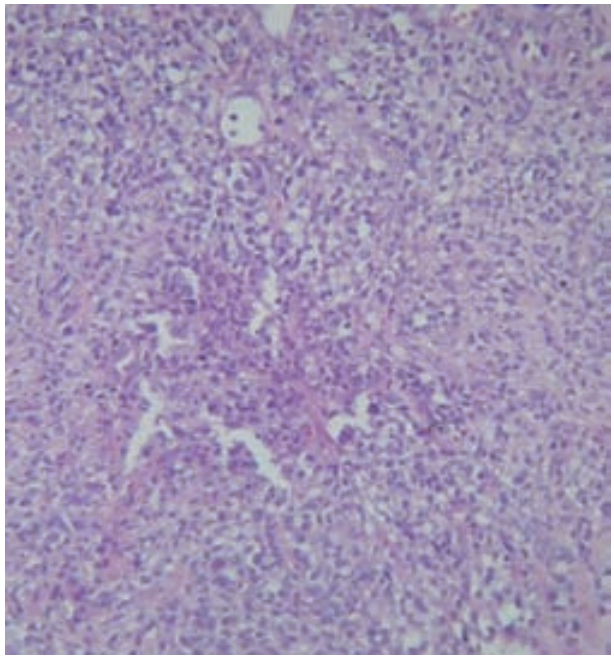

Figure 5
Lymphocytic infiltrates with some eosinophil granulocytes. Immunohistochemically: chronic macrophagocytic, histiocytic balanitis, fibrosing balanitis.

Figure 6
Status after a three-week therapy by doxycycline 2x100 mg. Full remission, discrete squamous formation during the recuperation process.

The question if the histopathological finding in this LGV-suffering patient is able to evolve into histopathological changes, jointly with other granulomatous diseases, such as pyoderma gangrenosum for instance, remains without answer [6]. This disease of unclear aetiology (pyoderma gangrenosum) initially shows neutrophilic infiltrates (acute stage), followed

by lymphocytic infiltrates (subacute stage), and granulomatous infiltrates (chronic stage) [6]. In another granulomatous disease, granuloma annulare, a full regression of the clinical diagram is frequently observed and the histological finding is within the evolution of the disease.

After a detailed analysis of all the bibliographic sources, we cannot totally exclude the hypothesis that the histopathological finding in LGV patients is able to evolve in accord with the clinicopathological finding. At the acute stage (case 1), the neutrophilic granulocytic infiltrates prevail; at the subacute stages probably the macrophagocytic and the histiocytic infiltrates do (case 2), while at the chronic stages the granulomatous infiltrates are probably predominant.

The surgical excision at stage 1b (patient 2) should not be recommended because of the fact that the lesions are of an ulceronecrotic nature and this would lead to the amputation of some part of the genital organs within the acute stage of the infection. Thus, it would not be possible to create optimal preconditions for a full restitution. Probably, dermatosurgery cannot be used as a primary or adjuvant method in patients suffering from LGV stage 1b or in patients with genital localisation of the initial ulcer papule. The reason is related to genital location and to the infiltrative plaque-like or endophytic growth of the lesions.

CONCLUSIONS

(1) A rare form of an extragenital form of lymphogranuloma venereum stage 1a is presented, clinically simulating spinocellular carcinoma with metastases in the lymphatic glands at the cervical area (Figs. 1a–1b). The role of dermatosurgery as an important supporting method in the initial stages of this disease is analysed and should be considered when lesions are located in the skin area and show a clinically clear delimitation from the healthy tissue.

(2) Another rare case of lymphogranuloma venereum localised in the glans penis area is described, under an atypical clinical diagram of a non-specific ulcerating balanitis (probably subacute stage) (Fig. 4).

(3) A rare and specific histological finding of ulcerating balanitis is described: macrophagocytic, histiocytic, fibrose reaction at LGV 1b stage. This shared finding is probably specific to the subacute stages of this disease. We do not exclude the possibility that ulcerating balanitis may be generated within the seropositive, active form of rheumatoid arthritis, which is frequently able to initiate non-specific skin and mucosa ulcerations. In this case, partial improvement can be achieved by the antiinflammatory effect of the antibiotics (immunomodulatory effect caused by doxycycline).

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SEVERE ROOT RESORPTION CAUSED BY ECTOPICALLY ERUPTING MAXILLARY CANINES: TREATMENT OPTIONS AND CASE REPORTS

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ABSTRACT

Root resorption of adjacent incisors caused by ectopically erupting canines is a well-known phenomenon. The purpose of this article was to discuss possible treatment methods in cases with severe root resorption. Three case reports are presented as examples of different procedures. All case reports describe the clinical appearance, radiographic evaluation and treatment procedure. The first case shows a treatment strategy involving the extraction of ectopic canine. Extraction of severely resorbed lateral incisors is depicted in the second case. The third case represents non-extraction orthodontic repositioning of the ectopic canine. CT examination was used for a precise diagnosis of root resorption and position of the ectopic canine. Indications, advantages, disadvantages and long-term results of three different treatment options are discussed.

INTRODUCTION

The maxillary permanent canine is the most frequently tooth to be ectopically erupting after the third molar with an incidence of 0.9% to 2.0% [1, 2]. Many studies have shown different occurrence between ethnic groups and gender [3, 4, 5, 6, 7].

The ectopically erupting maxillary permanent canine may cause root resorption of the adjacent permanent teeth. The progress of resorption is very rapid and asymptomatic. In a relatively short time, the resorption process may penetrate into the pulpal canal or result in reduction of root length [8]. This type of root resorption may occur early in life, already at the age of 9. However, Brown and Matthews [9] published a case report showing severe root resorption of a maxillary lateral incisor from a misplaced canine with the onset after 17 years of age. The data on the occurrence of root resorption caused by ectopically erupting canines reported in the published literature differ markedly. In 1956 Hitchin reported

Figure 1
Orthopantomogram of a 15-year-old girl. The upper left permanent canine is mesially inclined. The root apex of the upper left permanent lateral incisor is resorbed.

5 canines causing incisor root resorption in a sample of 109 impacted canines (4.6 %) [10]. Ericson and Kurol [11] conducted the radiographic study using the intraoral radiographs and polytomography. They showed that the root resorption of lateral incisors occurred in 12.5 % of ectopically erupting canines. Later, the same authors [12] used computerized tomography as a diagnostic aid for root resorption. They found that 48 % of ectopic canines caused root resorption of various depths and to various extents. Severe root resorption occurred in 22.8 % of lateral and 3.8 % of central incisors. Liu et al. [13] carried out a similar CT study of 210 impacted canines. They registered severe resorption in 10.9 % of canines, 5.2 % of lateral and 5.7 % of central incisors. Černochová et al. [14] in a sample of 334 ectopic canines found severe root resorption in 17.7 % of canines. Severe root resorption was present in 12.6 % of lateral incisors, 4.8 % of first premolars and 2.1 % of central incisors.

Ericson and Kurol [12] developed a grading system for the assessment of root resorption – no resorption (intact root surface), slight resorption (up to half of the dentine thickness to the pulp), moderate resorption (resorption midway to the pulp or more, the pulp lining being unbroken), severe resorption (the pulp is exposed by the resorption). Root resorption associated with the ectopic canine may affect various parts of the roots (apex, apical, middle and/or cervical root third). Natural healing of the lesions can be expected in cases with slight and moderate resorption. If the root resorption extends to the pulp, treatment is usually more complicated, expensive and time-consuming.

TREATMENT OPTIONS

The presence or absence of severe root resorption of the adjacent permanent incisor determines the appropriate treatment strategy of ectopic canines [15]. In cases with root resorption, the main principle of treatment is to eliminate the pressure of ectopic canines on the resorptive lesion as early as possible. When the canine is distanced from the resorbing area, resorption almost always stops [8].

Three possible treatment methods are available – extraction of an ectopic canine, extraction of a resorbed tooth, non-extraction orthodontic treatment. Each of them has its indications, advantages and disadvantages.

Extraction of the ectopic canine

Indications of extraction of the ectopic canine:

- general – extraction orthodontic cases (severe compression, high angle patients, etc.)

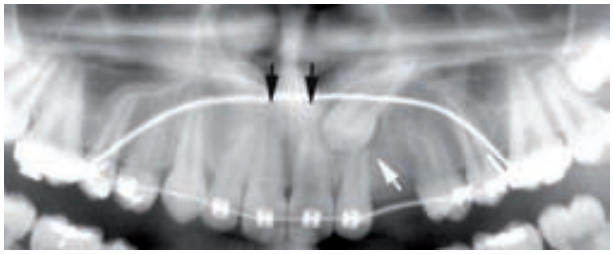
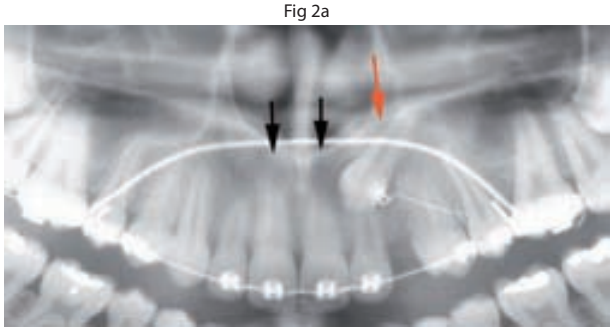


Fig 2a



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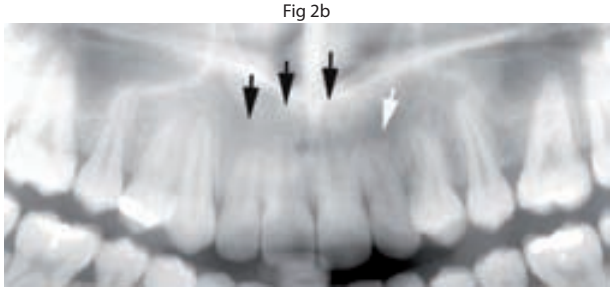

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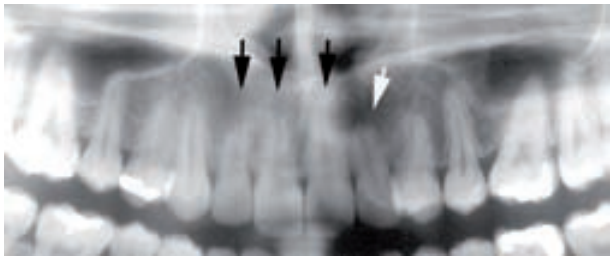

Fig 2d

Figure 2
Details of orthopantomograms. (a) At age of 15, before the second attempt at surgical exposure of ectopic canine. The apices of the upper central incisors (black arrows) are resorbed. The apex of the left lateral incisor (white arrow) is in close contact with the ectopic canine crown and is resorbed. (b) Six months after the second attempt of surgical exposure. The extent of the root resorption is without progression (black arrows). The position of the ectopic canine crown (red arrow) is more distal. (c) At age of 18, after debonding the fixed orthodontic appliance. The upper left lateral incisor (white arrow) has severe root resorption compared with other upper incisors (black arrows). (d) At age of 23, five years after debonding. There are no signs of progression of the resorption process.

- related to the ectopic canine – abnormal morphology, ankylosis, invasive external cervical resorption, internal resorption ("pink spot"), large follicular cyst, severely aberrant position

Advantages of extraction of the ectopic canine:
- Extraction of the ectopic canine causing root resorption of adjacent teeth means immediate and quick removal of the cause of resorption.
- This approach is usually simpler and less expensive than the others.
- All incisors remain preserved, thus the final outcome is naturally aesthetic.

Disadvantages of extraction of the ectopic canine:
- In some cases a healthy canine is extracted and a resorbed incisor is left in place. The long-term prognosis of this incisor is questionable.
- With a premolar in the canine position, the appearance may be compromised, and canine protection of the occlusion will not be present.

Extraction of the resorbed tooth

Indications of extraction of the resorbed incisor:
- general – extraction orthodontic cases
- related to the resorbed incisor – The incisor affected by the ectopic canine related root resorption may have poor prognoses. Root resorption process may lead to shortening of the root (i.e. increase in crown/root ratio), discolouration of the crown and loss of vitality.

Advantages of extraction of the resorbed incisor:
- Healthy canine is preserved.
- This treatment option is simpler than non-extraction orthodontic treatment.

Disadvantages of extraction of the resorbed incisor:
- The permanent canine is aligned in the extracted incisor site, with the accompanying compromised appearance and lack of a canine-protected occlusion.

Non-extraction orthodontic treatment

Indications of non-extraction orthodontic treatment:
- general – non-extraction orthodontic cases
- related to the ectopic canine – normal morphology of the ectopic canine without signs of pathology, favourable position for orthodontic repositioning

Advantages of non-extraction orthodontic treatment:
- The canine is brought to its place in the arch and canine-protected occlusion is maintained.
- All frontal teeth (canines and resorbed incisors) are preserved with normal, uncompromised appearance.

Disadvantages of non-extraction orthodontic treatment:
- Non-extraction orthodontic treatment is the most difficult method of treatment.

Figure 3
Intraoral views five years after completing the active orthodontic treatment. The canine protection of the occlusion is not present.

Figure 4
Intraoral views of a 14-year-old boy before starting the orthodontic treatment

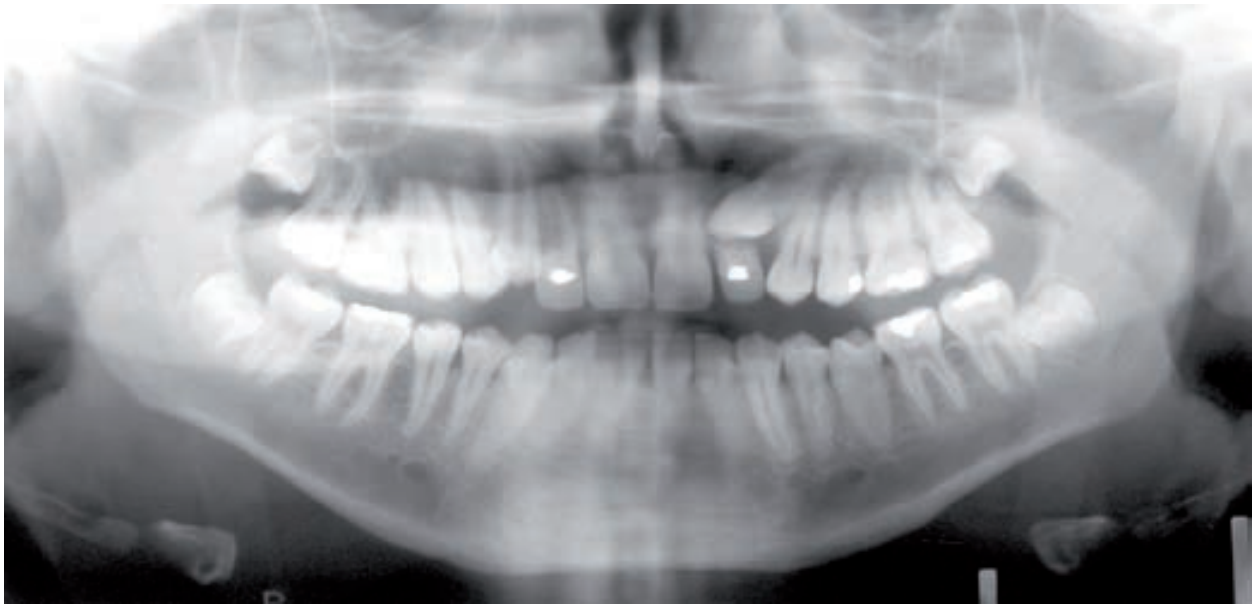

Figure 5
Orthopantomogram of a14-year-old boy before starting the orthodontic treatment

- The resorbed incisor is left in place with a questionable prognosis and outcome stability.

The purpose of the present article was to describe the above mention treatment options in three case reports and illustrate the long-term prognosis.

CASE REPORTS

Case 1

The first girl patient started her orthodontic treatment at 10 years of age. The patient had half unit class II, deep bite, diastema, distorotation of erupting upper permanent lateral incisors and loss of space for upper permanent canines. Her orthodontist placed a small fixed appliance with the aim to align the upper incisors and close the diastema. The transpalatal lingual arch was placed at 11 years of age before elimination of upper deciduous second molars. At 13 years of age, an orthodontist indicated the treatment with extraoral bow. Six months after the orthodontic treatment, 9 mm for eruption of upper right permanent canine and 6 mm for eruption of the left one were obtained. At 14 years of age the patient was reffered by her orthodontist to the Dental Clinic for surgical exposure of the upper left permanent ectopic canine crown. The surgeon took the palatal approach, but the canine crown was not found. After this unsuccessful attempt, the surgeon recommended an extraction or autotransplantation of the impacted canine. The patient and her parents chose the autotransplantation. This treatment required more open space in the upper left permanent canine region. The patient was referred by her orthodontist to the Orthodontic Department of Dental Clinic for continuation in treatment. The clinical orthodontist took orthopantomogram *(Figs. 1 and 2a)* and occlusal X-ray image and used the parallax method (vertical tube shift method) for localisation of the impacted canine crown. The buccal position of the left canine crown and the resorption of the apical root third of the left lateral incisor were determined. The treatment plan was changed to surgical exposure of the canine, bonding the attachment to the vestibular face of the canine and its orthodontic repositioning (open approach). The second attempt of surgical exposure by a buccal approach was performed at the age of 15. This procedure revealed a deep position of the ectopic canine crown, which was in intimate contact with the root of the lateral incisor. The attachment was bonded to the vestibular face of the canine, labial flap was sutured and the orthodontic traction was started. The orthopantomogram *(Fig. 2b)*, taken six months later, showed a small distal movement of the ectopic canine crown. However, no signs of the orthodontic repositioning of the ectopic canine were deternined during the next year. Therefore, the ectopic canine was surgically removed at the age of 17. The surgeon confirmed the ankylosis of the ectopic canine. The space in the canine region was closed by the mesially orthodontic movement of the upper left premolars and molars. The fixed orthodontic appliance was debonded at

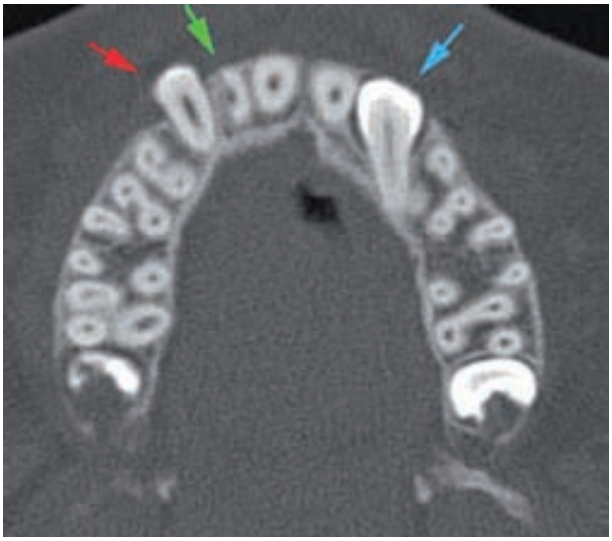

Fig 6a

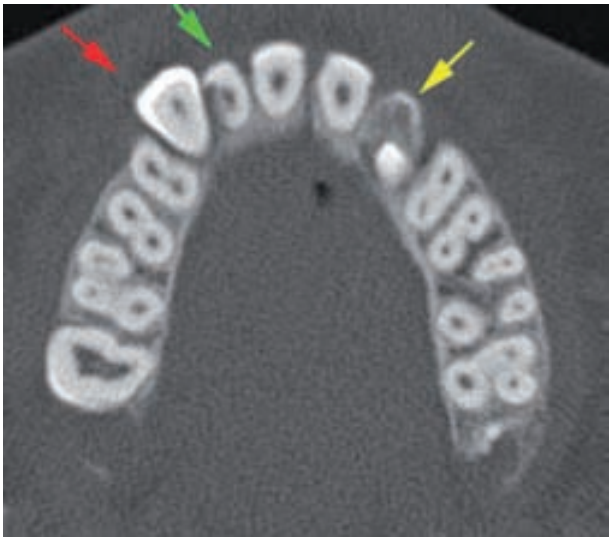

Fig 6b

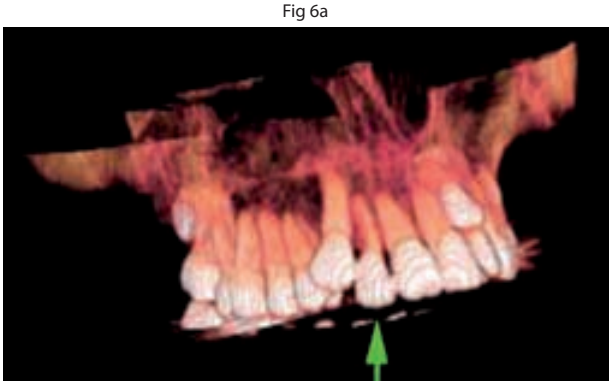

Fig 6c

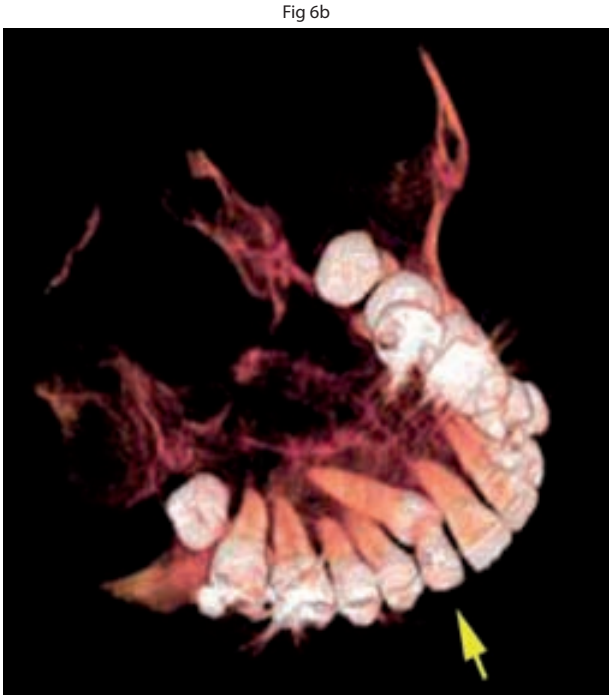

Fig 6d

Figure 6
CT views of a 14-year-old boy with the impacted upper permanent left canine. (a, b) Axial CT scans. (c, d) 3 dimensional images (volume rendering). The upper right canine (red arrow) is erupted buccally. The upper right lateral incisor (green arrow) has resorbed distal aspect of its root. The resorption involves the pulp in some areas. The upper left canine (blue arrow) is impacted and mesially inclined. The root of the upper left lateral incisor (yellow arrow) is completely resorbed.

the age of 18. Active treatment time extended over a period of 8 years. The orthopantomogram taken after active treatment revealed root resorption of the upper incisors *(Fig. 2c)*. The apical third of the left lateral incisor root was resorbed, resorption was related to the ectopic canine. At this time the upper left lateral incisor had normal mobility and was vital. The patient continued in treatment with the Hawley retainers. Five years after the active orthodontic treatment, the situation is stable *(Figs. 2d and 3)*.

Case 2

A 14-year-old boy was referred by his general dental practitioner for orthodontic treatment. He had a half unit class II on both sides. The upper and lower dental arches were crowded. There was a crossbite of premolars and the upper right lateral incisor. The overjet and overbite were reduced. The upper right canine was buccally placed. The upper left canine was still unerupted and not palpable. The upper left quadrant showed a total loss of space for the canine *(Fig. 4)*.

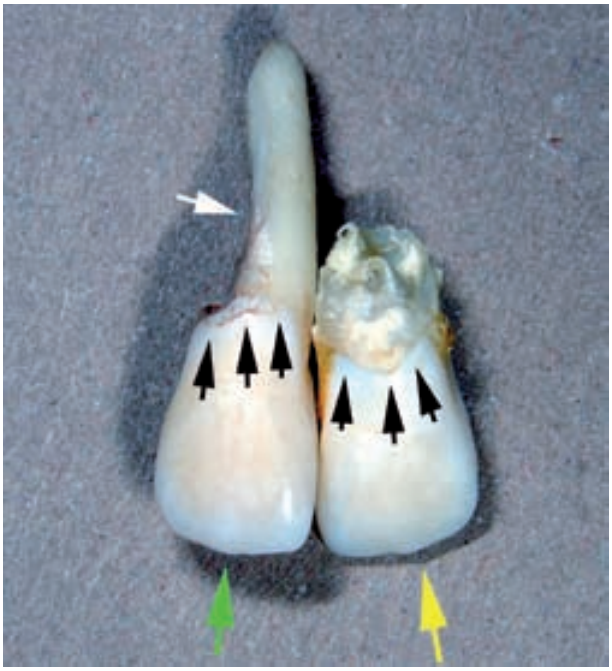

Figure 7
Frontal view of the etracted upper lateral incisors. The right incisor (green arrow) has severely resorbed the distal aspect of root with penetration in the pulpal canal (white arrow). The root of the left incisor (yellow arrow) is completely lost. The enamel of both incisors is also resorbed (black arrows).

The orthopantomogram *(Fig. 5)* confirmed the presence of all permanent teeth and unusual appearance of the distal aspect of the upper right lateral incisor root. The upper left canine was mesially inclined. The root of the upper left lateral incisor was not clear. Root resorption of both upper lateral incisors was considered and CT examination was performed *(Fig. 6)*. The CT examination showed the severe root resorption of both upper lateral incisors. The root of the left lateral incisor was completely resorbed. The prognosis for the upper lateral incisors was poor. Cephalometrically, the patient had a Class I skeletal relationship (ANB angle = 1.5°, Wits appraisal = –2 mm), an increased lower anterior facial height and a counterclockwise (backward) rotation of the mandible. Based on the patient´s overall analysis, an extraction orthodontic treatment plan was chosen as the most appropriate treatment approach. In the surgical phase of treatment, the both upper lateral incisors were extracted and the upper left canine was exposed. The extracted upper lateral incisors were found to be severely resorbed *(Fig. 7)*. The upper canines were orthodontically moved into place of the lateral incisors *(Figs. 8–9)*. The patient and his parents refused the placement of a fixed orthodontic appliance in the lower dental arch. Active orthodontic treatment was finished after 24 months with the understanding that treatment was incomplete. Esthetic recontouring of the canine crowns and extraction of lower third molars were recommended. The maxillary Hawley retainer was placed. The patient compliance was poor, he did not continue to wear the retainer.

Case 3

The third patient was a 15-year-old girl, who was referred by her general dental practitioner due to impaction of the upper left permanent canine. The molar relationship on the right side was normal and there was a half unit class II on the left. The upper left first molar was in crossbite. The upper left deciduous canine was missing. The upper arch was well aligned *(Fig. 10)*. Mild (<3mm) crowding was present in the lower arch. The orthopantomogram *(Fig. 11)* showed the presence of all permanent teeth. The third molars were unerupted. The upper left permanent canine appeared mesially inclined. The apical areas of the upper left central and lateral incisors were not clear. The possibility of root resorption was considered and CT examination was indicated. The CT examination *(Fig. 12)* revealed severe resorption of the apical root third of the upper left permanent lateral incisor. After a discussion with the patient and her parents, the orthodontic treatment was started with the aim to upright orthodontically the ectopic canine and to bring it to its correct position. The transpalatal lingual arch according to Burstone (0.032 x 0.032, TMA, ORMCO) was placed for correction of mesial rotation and crossbite of the upper left first molar. Six months later, the transpalatal lingual arch was exchanged for a stainless steel lingual arch with arm (0.032 x 0.032, stainless steel, ORMCO). The maxillary left canine was surgically exposed with an open approach and orthodontically moved away from the incisors. The upper fixed orthodontic appliance [18-slot bracket, OmniArch, GAC) was bonded four months after canine exposure. The wire sequence was – 0.012 round ECO-Nitanium (LPI), 0.016 x 0.016 rectangular NeoSentalloy (GAC), 0.016 x 0.022 rectangular TMA (ORMCO) arch with "T" loop for opening space for left canine, 0.017 x 0.025 rectangular TMA (ORMCO) cantilever with "box" loop for buccal movement of the palatally placed canine, 0.016 x 0.022 rectangular TMA (ORMCO) arch with two "L" loops for canine root torque *(Fig. 13a)*, 0.016 x 0.022 rectangular stainless steel (GAC). Active treatment time was 38 months. After removal of the fixed appliance, the upper Hawley retainer was delivered. The patient did not have any clinical symptoms of pulpal sensitivity of the upper left incisors during active orthodontic treatment and after this treatment both upper left incisors had normal mobility. However, the left canine had increased mobility in the horizontal direction *(Fig. 13b)*. The dehiscence of the cervical area of the palatal surface of the canine root was apparent *(Fig. 14)*.

Figure 8
Views of a 16-year-old boy after completing the active orthodontic treatment

The orthopantomogram showed bone loss around the upper left permanent canine. The apical root third of the upper left lateral incisor was resorbed. Also the apex of the upper left central incisor was slightly resorbed. The state is stable after sixteen months *(Figs. 13c, 14–15)*. However, the periodontal treatment was recommended.

DISCUSSION

The exact etiology of root resorption related to ectopically erupting canines is not clearly understood. Several possible causative factors have been considered, such as pressure and inclination of an erupting canine, follicular activity, orthodontic forces, genetic factors, trauma, developmental insufficiencies of immature roots and their susceptibility to the resorptive enzymes [3, 16, 17, 18, 19]. It has been shown that elimination of pressure between the ectopic canine and affected roots stops the resorptive processes. Our clinical experience confirms this opinion. Our first case report demonstrates no progression of root resorption of the lateral incisor after the extraction of the ectopic canine. In the third case report, the treatment approach was based on orthodontic traction directing the canine from resorbing roots. The resorptive process was also halted. Orthodontic movement of the affected tooth can start after the elimination of contact between the canine crown and resorbing root [8]. This is the essential condition for halting of resorption.

However, root resorption is known to occur as a result of the application of orthodontic forces [20]. Several patient-related or treatment-related factors associated with root resorption have been discussed in the literature. One of the treatment-related factors is the duration of treatment. Nevertheless,

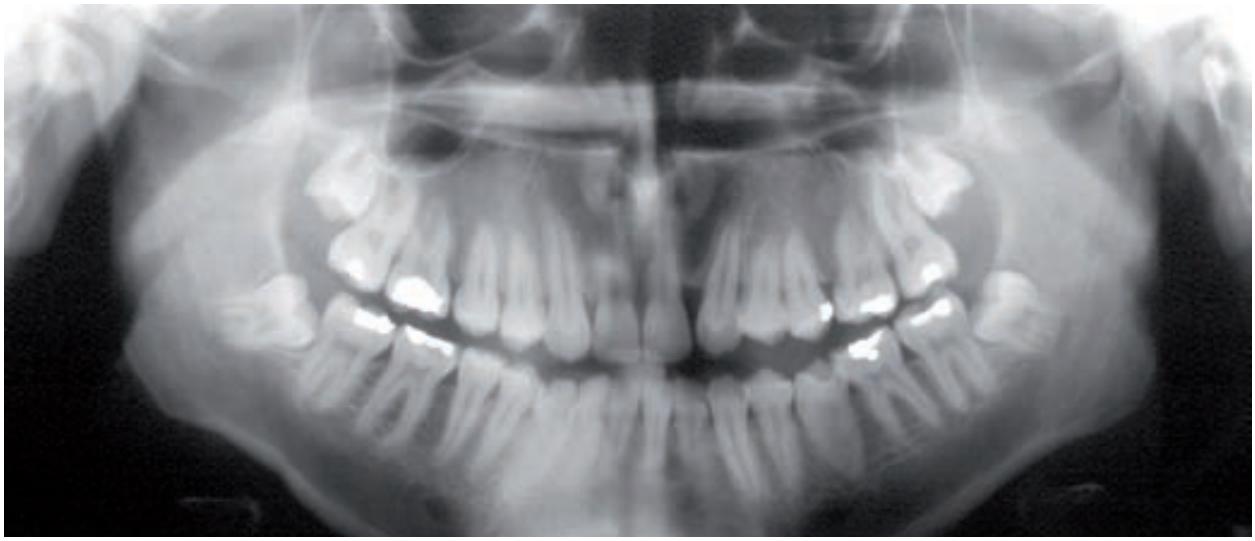

Figure 9
Post-treatment orthopantomogram. Both upper canines show good root alignment

Figure 10
Intraoral views of a 15-year-old girl before starting the orthodontic treatment

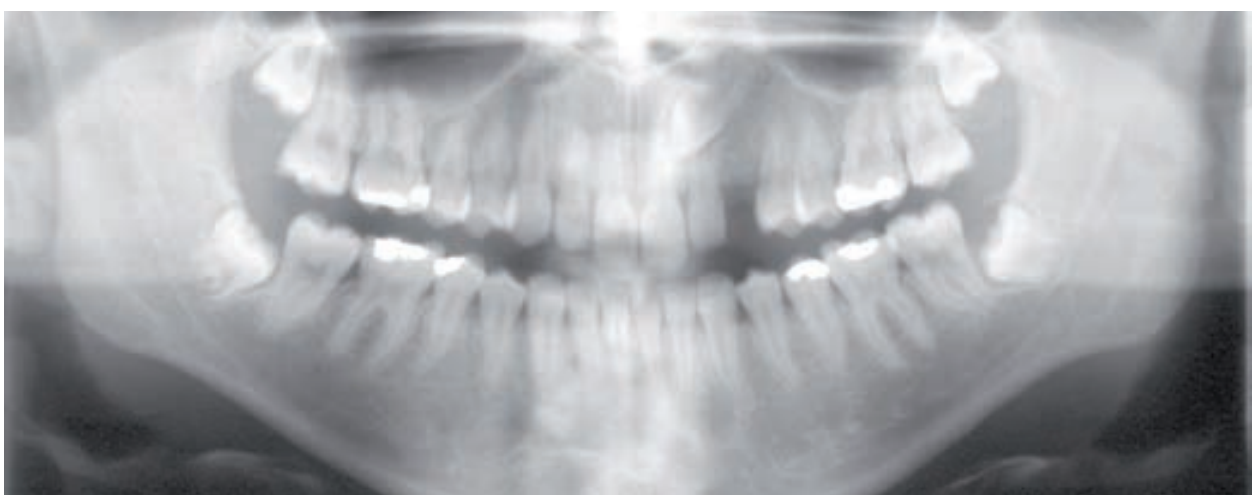

Figure 11
Orthopantomogram of a 15-year-old girl before starting the orthodontic treatment

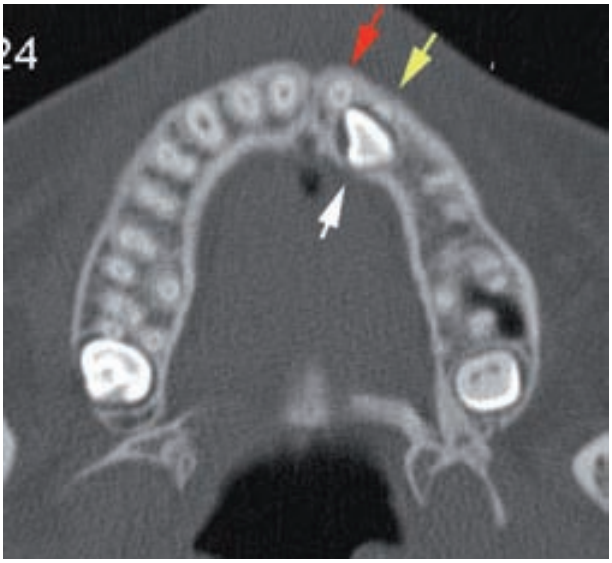

Fig 12a

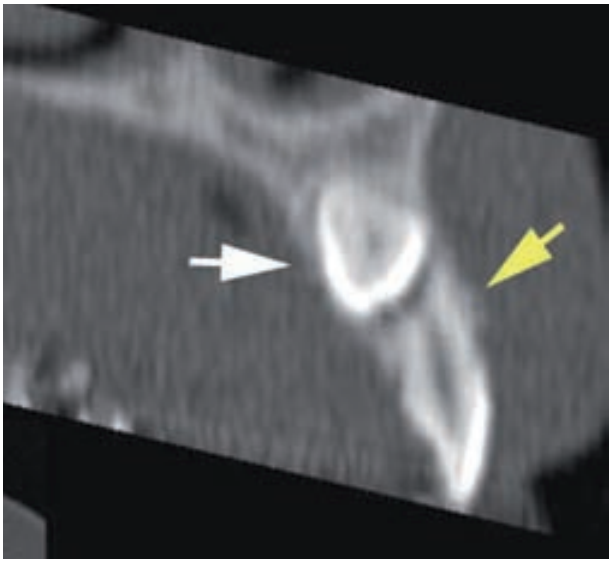

Fig 12b

Fig 12c

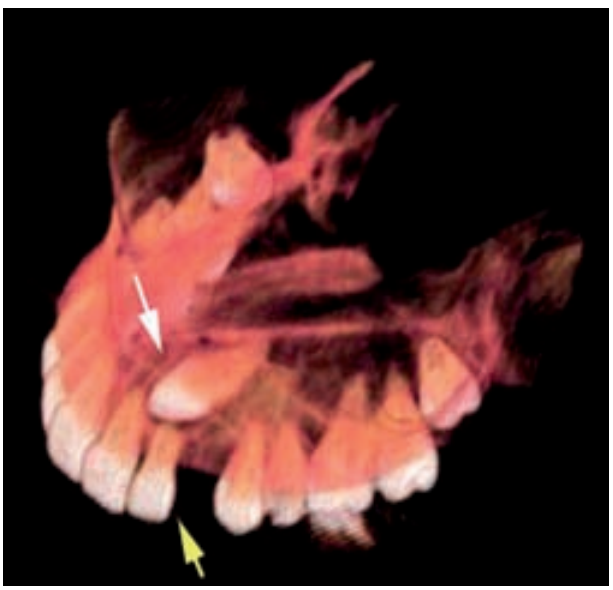

Fig 12d

Figure 12
CT views of a 15-year-old girl with the impacted upper left permanent canine. (a) Axial CT scan. (b) Multiplanar reconstruction (MPR) in plane cutting through the long axis of the affected lateral incisor. (c and d) Three-dimensional views (volume rendering). The crown of the impacted upper left permanent canine (white arrow) is located palatally to the dental arch. The apical root third of the upper left permanent lateral incisor (yellow arrow) is resorbed. The root of the upper permanent left central incisor (red arrow) is without resorption.

prolonged duration of treatment does not necessarily coincide with the extended period of the application of active orthodontic forces [21]. The very prolonged duration of active treatment, showed in the first case report, confirms this opinion. The external apical root resorption of the upper central incisors was apparent already after the levelling phase of treatment.

The early detection and treatment of root resorption caused by ectopically erupting canines is indicated due to its rapid and asymptomatic progression. This type of root resorption is known to lead to extensive damage to root of adjacent permanent teeth. In the second case report, the left ectopic canine caused total loss of root of lateral incisor. Resorption in this case was very extensive. Also the enamel of both incisors was resorbed. The considerable extents of root resorption and extraction orthodontic cases are the main indications supporting extraction of resorbed teeth treatment approach.

A review of the literature shows only little evidence about the long-term survival of teeth affected by root resorption associ-

Fig 13a

Fig 13b

Fig 13c

Figure 13a
Intraoral view five months before completing the active treatment. Two "L" loops are used for the torque movement of the canine root (white arrow)
Figure 13b Intraoral view after debonding the fixed orthodontic appliance. The upper left lateral incisor (yellow arrow) and canine (white arrow) are in good periodontal state
Figure 13c Intraoral view sixteen months after active orthodontic treatment. Situation is stable

Figure 14
Intraoral views on the upper dental arch five months before (a) and sixteen months after completing the active treatment (b). The dehiscence of the cervical area of the palatal surface of the canine root is evident (white arrows)

ated with an adjacent ectopic canine. Becker and Chaushu [8] reported fairly good long-term prognoses of resorbed incisors. At the post-treatment follow-up, the resorbed incisors were not discoloured and unduly mobile and did not require permanent splinting. The root canal treatment for reducing further resorption is inappropriate. Falahat et al. [19] evaluated the resorbed incisors during a 2- to 10-year follow-up period. They also confirmed good long-term healing of resorbed incisor roots. We showed good long-term prognoses of incisors with root resorption related to the ectopic canine in our first and third case

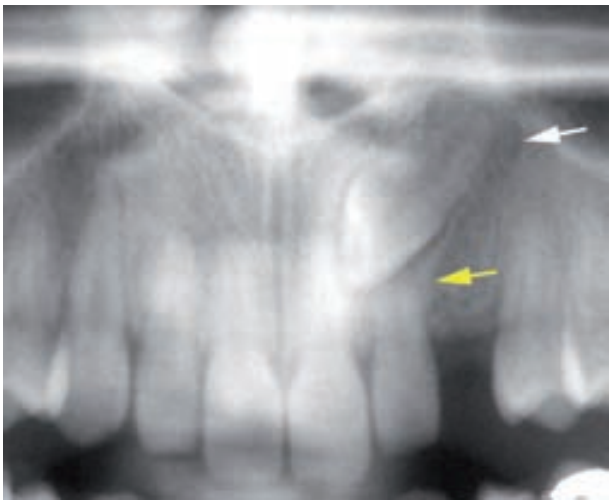

Fig 15a

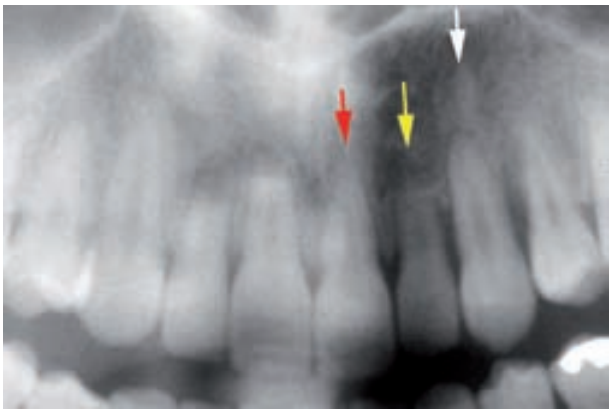

Fig 15b

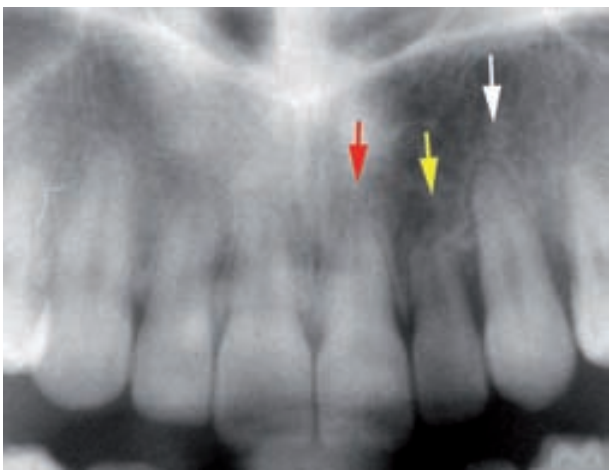

Fig 15c

Fig 15d

Figure 15a
Detail of pretreatment orthopantomogram (OPG). The impacted upper left permanent canine (white arrow) is mesially inclined. The root apex of the upper left lateral incisor (yellow arrow) is not clear.
Figure 15b Detail of post-treatment OPG. The upper left canine (white arrow) is aligned within the dental arch. The bone loss around this tooth is apparent. The upper left lateral incisor (yellow arrow) has resorbed the apical third of its root. Slight apical resorption of the upper left central incisor (red arrow) is evident.
Figure 15c Detail of OPG and Figure 15d periapical radiograph illustrating 16-months post-treatment situation. The root resorption of incisors and the bone loss around the canine remain stable.

reports. The signs of healing process, such as the radiographic reappearance of an intact lamina dura, periodontal ligament and bony trabeculation in the periapical area, are evident on radiographs. The affected incisors have normal colour and mobility and are vital. Gathered evidence suggests that there are few reasons for automatic indication of extraction of resorbed teeth. Moreover, severely resorbed teeth may function as natural space maintainers during the growth period.

The first and third case reports show that the treatment approach with the aim to correct ectopic canine position orthodontically is usually time-consuming. Selection of this treatment approach is supported by the opinion that the canine in its position has an important role in the establishment of a good functional occlusion. However, in the first case, the canine had to be extracted due to the ankylosis. The overall treatment duration was excessively long. The treatment pro-

cess was influenced by the excessive effort to preserve the canine. Becker [3] emphasized that clinicians must carefully assess the long-term prognoses of an impacted canine before treatment in each individual case. It is very important to decide which canines will take excessive long treatment time or which will be adversely affected in periodontal terms. In the third case report, recession of the cervical area of the palatal mucosa of the canine was present. It is known that this recession occurs secondary to an alveolar bone dehiscence. The bone support of the orthodontically moved impacted canine may be adversely affected by several factors, such as ectopic position of the canine, surgical exposure, root uprighting and torque movements and oral hygiene during the traction period. A number of movements are required for repositioning of the ectopic canine – tipping, rotation, torque, bodily and eruptive movements. The magnitude of necessary force can be great. The excessive force can create periodontal ligament hyalinization. Especially, the tipping forces can cause hyalinized areas in the periodontal ligament at the level of the alveolar crest [22]. It has been shown that radical surgical exposure in which the follicular sac was removed down to the cemento-enamel junction leads to less bone support. The crestal bone level is higher when ectopic canine is minimally exposed. The inadequate plaque control of the exposed ectopic canine results in the presence of putative periopathogenes. Interaction of the above mentioned factors probably caused periodontal damage observed in the third case report.

CONCLUSIONS

The choice of the treatment approach is influenced by the presence of ectopic eruption of the upper permanent canine, root resorption of adjacent permanent teeth and other orthodontic anomalies. The clinician must carefully assess all the factors that can affect long-term prognoses of the results of the treatment in each individual case. In these cases, CT examination is indicated. CT axial scans and 3D reconstructions reveal an extent and location of root resorption. Knowledge of the exact position of the ectopic canine allows a surgeon to minimize surgical procedure and enables an orthodontist appropriate orthodontic movements.

ACKNOWLEDGEMENTS

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NON-SURGICAL TREATMENT OF THREE- AND FOUR-PART PROXIMAL HUMERAL FRACTURES IN ELDERLY PATIENTS

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ABSTRACT

Background: We assessed the clinical and radiological outcome of non-surgical treatment in elderly patients with displaced three- and four-part fractures of the proximal humeral head. **Methods:** Between 2003 and 2005, 47 patients (41 females and 6 males) with a mean age of 79.2 years (range 62–99 years) at the time of injury were treated non-surgically for a three- or four-part fracture of the proximal humerus with a Gilchrist bandage. In a two-year period a total of 550 patients were seen for a fracture of the proximal humerus at our institution, 313 with a three- or four-part fracture. Altogether 133 patients underwent surgery, 180 were treated non-operatively, whereas 133 were lost to follow-up. The average follow up was 26.4 months (range 14–41 months). Absolute and relative Constant Score was used to assess the clinical outcome. To identify differences in the clinical outcome, patients with three-part fractures were compared to those with four-part fractures, concerning gender, age (younger than 75 years and older than 75 years), and CS. Radiographs were taken to determine fracture classification according to the system by Neer and to assess fracture healing.

Results: At the time of follow-up, the mean Constant Score was 66.7 for the three-part group and 58.2 for the four-part group. Overall, 32 (78.1 %) patients showed excellent, 6 (12.8 %) good, 3 (6.3 %) moderate, and 6 (12.8 %) patients poor results. Forty-two patients reported that they were satisfied with their shoulder function, 16 (34 %) shoulders had pain, 4 (9 %) graded as moderate, and 12 (25 %) as mild. Physical therapy was performed in 32 patients. Forty-five (95.7 %) shoulders healed radiographically. One shoulder had evidence of avascular necrosis of the humeral head and non-union occurred once. Seven shoulders had an acceptable alignment during follow-up. There was no significance between the two fracture types concerning Constant Score ($p = 0.083$). Only age revealed to be statistically significant ($p = 0.003$).

Conclusions: The results from this study suggest that non-surgical treatment of displaced proximal humeral fractures in elderly patients should be considered as a treatment option, especially in those patients in which medical circumstances do not allow an operative treatment.

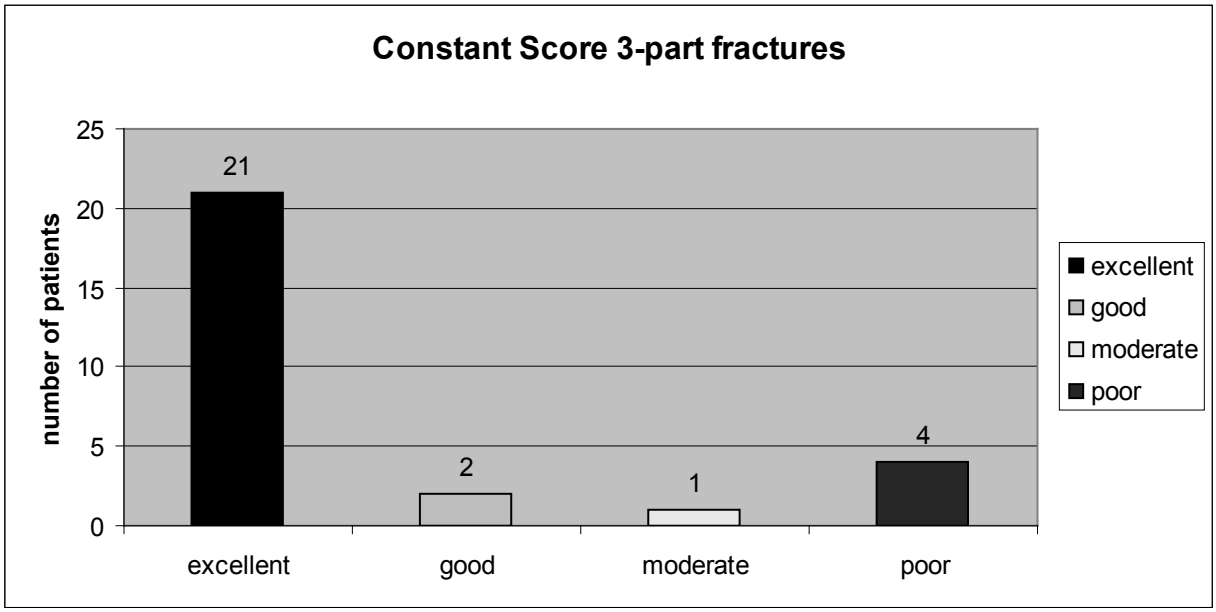

Figure 1
Constant Score in 4-level scale in patients with 3-part fractures

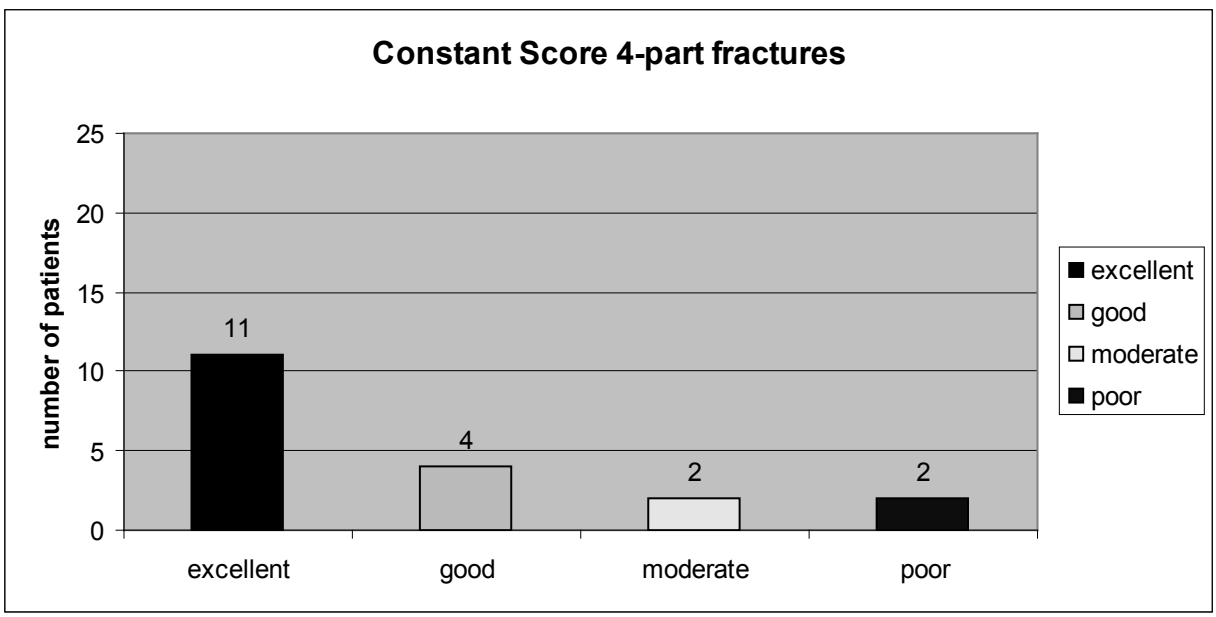

Figure 2
Constant Score in 4-level scale in patients with 4-part fractures

INTRODUCTION

Proximal humeral fractures account for 4 % to 5 % of all fractures and most commonly affect elderly patients with osteoporotic bone [1]. These fractures usually result from a fall onto an outstretched arm [2]. Women are twice as likely to be affected as men [2]. During the last years different classification systems have been presented. The Neer's system was published in 1970; it is based on an anatomic segmental classification, and has been widely accepted [3]. It is well established that two-part fractures and fractures with minimal displacement are successfully treated conservatively [3–5]. Elderly patients with comminuted displaced fractures present an increased treatment problem. These three- and four-part fractures represent 13 % to 16 % of all proximal humeral fractures [3]. The management of these fractures remains controversial [6–13]. For selection of the optimal treatment, the general condition of the patient, additional injuries and chronic diseases have to be assessed as well as the patient's compliance that might limit rehabilitation and personal demands. One major problem in surgical treatment is the high incidence of osteoporotic bone not allowing stable internal fixation and early active exercises. Further numerous medical comorbidities can prohibit surgical intervention and affect the outcome of these injuries in increasing the incidence of delayed union or non–union. Many surgical treatment techniques and fixation methods have been used to treat displaced proximal humeral fractures, including plates, screws, pins, intramedullary nails, either isolated or in combination, and arthroplasty [2,5]. The results vary from excellent to poor [5,7,10]. Surgical treatment of proximal humeral fractures, especially in elderly patients with poor bone quality in combination with a thin or ruptured rotator cuff, is associated with a high frequency of complications and an unpredictable end result [8]. Some studies show acceptable outcomes after conservative treatment of three- and four-part fractures [8,10].

The purpose of this study was to assess the clinical and radiological outcome after non-surgical treatment of three- and four-part fractures of the proximal humerus in elderly patients. Furthermore, we compared the functional results in relation to fracture type (three-part or four-part fractures).

MATERIAL AND METHODS

From July 2003 until June 2005 a series of 47 patients aged 60 years or older with three- or four-part fractures of the proximal humerus, not caused by high-energy trauma or pathological, were evaluated following non-surgical treatment of their injury. In a two-year period a total number of 313 patients aged over 60 years were seen at our institution with a three- or four-part fracture of the proximal humerus. Altogether, 133 patients underwent operative treatment (including plate fixation and arthroplasty) and 180 patients were treated non-operatively. According to our treatment protocol patients with three- and four-part fractures of the proximal humerus usually undergo surgical treatment by plate fixation or hemiarthroplasty. The only excluding factor was an increased anaesthesia risk (ASA 3 and 4), as in 180 patients of our series. Altogether, 133 patients were lost to follow-up; 42 patients had died, 21 patients had moved, 10 were not registered, 15 patients were tourists and lived abroad. The remaining 45 patients were contacted by telephone: 20 patients did not reply and the other 25 patients refused to appear for examination. Two groups were created: patients with 3-part fractures (n = 28, mean age 76 years) and those with 4-part fractures (n = 19, mean age 83.9 years).

The injured arm was supported in a Gilchrist bandage for 3 weeks, followed by physiotherapy in some cases. In the Gilchrist bandage the lower and upper arm are fixed in

Figure 3
The X-ray was classified as a 3-part fracture (white arrows) of the proximal humerus at the time of injury; 91-year-old woman

Figure 4
The X-ray of the 3-part fracture from Figure 3 two years after injury; fracture healed, a moderate osteoarthritis was found and axial alignment was between 80° and 100°, more than 1 cm displacement of greater and less tubercle, humeral shaft in contact, but varus impaction
Absolute Constant Score: 82

a bandage, while the elbow joint is in 90-degree flexion and banded to the side [14]. All patients were assessed clinically and radiologically. Clinical examination was performed with the use of the absolute and relative Constant scoring system at follow-up by one of the two senior authors [14–16]. X-rays were also assessed by one of the senior authors, both experienced shoulder surgeons, at the time of follow–up (ranging from 14 to 41 months). Constant Score has been used widely for almost 20 years in the assessment of the clinical outcome after shoulder procedures. It is a simple clinical method of shoulder functional assessment that allows the evaluation of the overall function as well as of the individual parameter. It is easy to use in clinical setting and is also reproducible, and takes only a few minutes to perform. In the assessment of shoulder function it is essential to consider gender, age, and activity level. The CS takes this into account. A maximum of 100 points can be achieved in this functional assessment. The patients were asked if they could accept their shoulder conditions. The subjective parameters assess the degree of pain and the ability to perform the normal tasks of daily living. The objective parameters are based on the active range of motion and shoulder power. Constant Score was categorised on a four-level scale as excellent results (100–86 points), as good (85–71 points), moderate (70–56 points), and poor results (< 55 points).

The Relative Constant score represents the absolute CS score of an individual patient in relation to her/his healthy shoulder in percentage [17].

Shoulder pain was categorised by patients as none (15 points), mild (10 points), moderate (5 points), or severe (0 points).

Muscle strength was measured using a tension spring balance with a digital readout with the shoulder in 90° abduction and the elbow in 90° flexion. An average of three repeated tests was calculated. The strength of the contralateral shoulder was also measured. For each half kilo 1 point is scored; a maximum of 25 points can be achieved altogether.

The activities of daily living which were assessed included ability to work (4 points), leisure or sports activities (4 points), and undisturbed sleep (2 points). Further positioning of the hand was included: up to the waist (2 points), up to the xiphoid (4 points), up to the neck (6 points), up to top of the head (8 points) and above the head (10 points). A maximum of 20 points could be achieved.

Painless range of motion in the glenohumeral joint in flexion, abduction, internal and external rotation was measured with a goniometer. Ten points for each part of the functional shoulder motion were allocated. In this part a maximum of 40 points could be achieved.

Concerning radiological assessment, radiographs at injury were used to classify the fracture type. At the time of injury CT-scan was not included in our standard protocol for classifying proximal humerus fractures at our institute. The Neer classification was used and only three and four-part fractures were included in our study.

At the follow-up, radiographs were taken in two planes, anterior to posterior and axial. The occurrence of necrosis and non-union was noted. Furthermore, the degree of osteoarthritis was determined using three grades: 1 None, 2 Moderate – less than 50 per cent narrowing the joint space and peripheral osteophytes, 3 Severe – more than 50 per cent narrowing joint space.

In addition, axial alignment was determined using a four-graded scale: (1) less than 50° – minimal displacement of the bone fragment, (2) between 50° and 80° – both tubercles in place and varus impaction, (3) 80° and 100° – more than 1 cm of displacement of greater or less tubercle, humeral shaft in

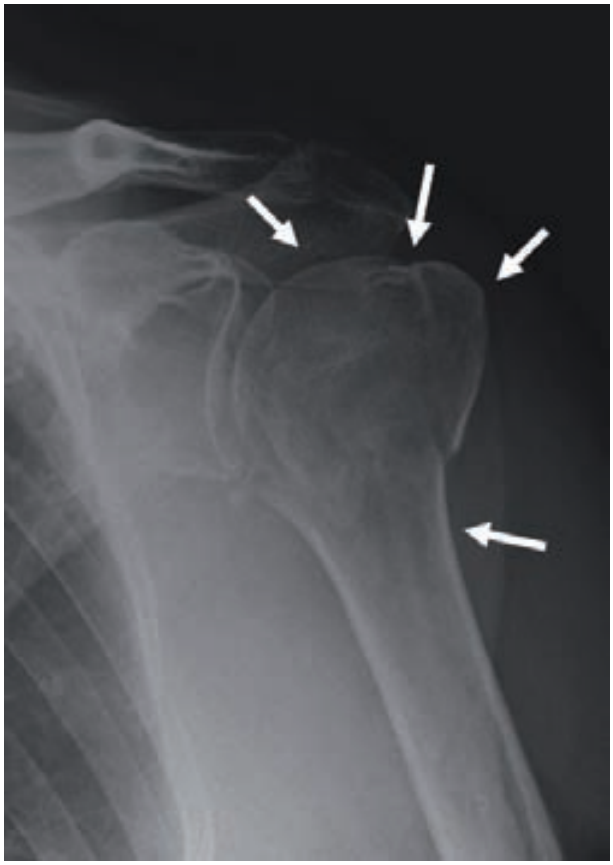

Figure 5
The X-ray was classified as a 4-part fracture (white arrows) of the proximal humerus at the time of injury; 62-year-old woman

contact with humeral head but varus or valgus impaction, (4) more than 100° – humeral head no contact with humeral shaft.

STATISTICAL ANALYSIS

All statistical analysis was performed by the Institute for Medical Statistics, situated at the Vienna Medical School. To identify differences in the clinical outcome, patients with three-part fractures were compared to those with four-part fractures. The factors being analysed in this study were age, gender, Constant Score, pain, strength, activities of daily living, and range of motion. For univariate analysis we performed a Student's t-test. Statistical significance was defined with a p-value of $p < 0.05$. For variables that showed statistical significance in the univariate analysis, we performed multivariate analysis additionally.

RESULTS

The study group consisted of 48 patients: 41 (85.1 %) females and 7 (14.9 %) males. The mean age at the time of injury was 79.2 years (ranging from 62 to 99 years, median = 80). Forty-six patients were already retired. Mean follow-up was 26.4 months (ranging from 14 to 41 months, median = 25). Twenty-eight (59.6 %) patients were treated for a three-part fracture (mean age was 76 years, ranging from 62 to 88 years, median = 78.5), and 19 (40.4 %) patients for a four-part fracture (mean age was 83.9 years, ranging from 62 to 99 years, median = 86). Fracture occurred 17 times at the dominant arm. Thirty-two patients had physical therapy with a minimum of 10 cycles.
Mean Constant Score was 72.3 for the non-affected shoulders and 63.3 for the fractured shoulders. We had a relative Constant for the fractured shoulder of 87.7 %. Overall, 32 (68.1 %) patients showed excellent results, 6 (12.8 %) patients good results, 3 (6.3 %) patients moderate, and 6 (12,8 %) patients poor results.
In the three-part fracture group the Constant Score for the non-affected shoulder was 76.3 and 66.7 (median = 72) for the fractured shoulders. Relative Constant Score was 87.4 %. The results were graded as excellent in 22 (75 %) patients, good in 2 (7.1 %) patients, moderate in 1 (3.6 %), and poor in 4(14.3 %) patients (Figure 1).
In the four-part fracture group the Constant Score for the non-affected shoulder was 66.4 and 58.2 (median = 59) for the fractured shoulder. Relative Constant Score was 87.7 %. The results were graded as excellent in 11 (58 %) patients, good in 4 (21.1 %) patients, moderate in 2 (10.5 %), and poor in 2 (10.5 %) patients (Figure 2).
Forty-two (89.4 %) patients reported that they could accept their shoulder condition.

Pain:
Sixteen patients reported pain: 12 mild and 4 moderate. In the three-part group the mean Constant Score was 12.8 and in the four-part group 12.6 (Table 1)

Muscle strength:
In the 28 shoulders of the three-part group the mean Constant Score for this part was 5.9 and in the 19 shoulders of the four-part group 4.9 (Table 1). For the contralateral shoulders the mean Constant Score was 8.1 in patients with three-part fractures and 6.7 in patients with four-part fractures.

Activities of daily living:
Scoring of the ADL-function gave a mean value of 17.0 points in the three-part group and 15.2 points in the four-part fractures group (Table 1).

Figure 6
The X-ray of the 4-part fracture from Figure 5 two years after injury; fracture healed and axial alignment was between 50° and 80°, both tubercles in place and varus impacted.
Absolute Constant Score: 71

Range of motion:
Mean Constant Score for flexion, abduction, internal and external rotation was 30.8 in patients with three-part fractures and 24.5 in those with four-part fractures of the humeral head (Table 1).

Radiographic assessment:
In 45 cases fracture healing could be achieved. In one three-part fracture non-union was found and in one four-part fracture osteonecrosis was observed. Osteoarthrosis was found in 3 cases: One mild and one moderate osteoarthrosis occurred in the three-part fracture group. Severe osteoarthrosis was observed in one case (four-part fracture). The position was good in 7 cases. Axial malalignment was identified in 40 cases: < 50° in 20 patients, 50°–80° in 14 patients, 80°–100° in 4 patients, and > 100° in 2 of our patients (Figures 3 to 6).

DISCUSSION

Fractures of the proximal humerus are found most frequently in elderly patients with osteoporotic bones. Some of these fractures can heal without significantly impaired shoulder function, and sometimes even rather complex fractures will have a satisfactory outcome.
In the present study we used the relative Constant Score, because it is essential for shoulder function to consider gender, age and activity level. Discrepancy occurred between a low Constant Score and the patient's own opinion of their shoulder situation. Forty-two patients (89.4 %) were satisfied with their shoulder function. Probably, the high acceptance rate can be explained by the minor persistence of pain. Elderly patients are satisfied if they could range their normal activities of daily living, such as cooking or housekeeping, and priorities seem to switch in geriatric patients. Relative Constant score did not show any differences between 3- and four-part fractured shoulders. When graded, excellent results were seen more commonly in patients with three-part fractures. There was a significant difference in age, possibly influencing the functional end result. Early mobilisation and physiotherapy in nearly all cases might also be an explanation for the patients' satisfaction with their shoulder function. Less pain, especially in the elderly, also seems to be a factor which leads to more satisfaction, even if the ROM is decreased.
There was no relationship between the radiographic and clinical outcomes. Both the one patient with osteonecrosis and the one patient with severe osteoarthrosis could accept their shoulder function. The radiographic findings seem to have no influence on the clinical outcome of patients. Elderly patients seem to adapt well to the damaged shoulder in daily life. Although the outcome for four-part fractures was less than for three-part fractures, non-operative treatment minimises the complications which can appear in surgery. Furthermore, complete recovery cannot be confirmed with surgery, either, as seen in some studies.
All the other variables did not show any statistically significant differences. Both univariate and multivariate analysis revealed that only "age" had a significant influence on the clinical outcome referring to the fracture type.
A report of 15 patients with comminuted fractures of the proximal humerus treated conservatively showed similar results, with a Constant Score of 59 (three-part fractures) and 47 in the four-part fracture group, respectively [1]. All patients reported that they could accept their shoulder function [1]. We found a good functional outcome with only moderate or mild pain and an acceptable shoulder condition for most of the patients after non-operative treatment.
Our findings support the data with Zyto et al., who randomised 40 elderly patients to either conservative or tension-

band osteosynthesis. The clinical outcome of surgical treatment was similar in comparison with conservative treatment, and more complications are found in the surgically treated group [8].

Ilchmann et al. compared non-operative treatment versus tension-band osteosynthesis in three- and four-part proximal humeral fractures and found poor results for four-part fractures after non-operative treatment; however, the differences were not significant [10]. Four-part fractures are still a clinical challenge leading to poor function and a high risk of osteonecrosis because of damages to the vascular supply of the displaced head fragment [18,19].

In 30 patients (63.8 %) fracture occurred affecting the non-dominant arm. This circumstance might be an explanation of why most of the patients were satisfied with their shoulder function and daily living activities of the patients could be carried out without pain. The fracture did not seem to bother them because the patients used the non-affected shoulder for their activities.

The variety of treatment options and results indicates that no clear guidelines are available. Examples of this are the findings in our patients with the three-part fractures in which moderate pain occurred as well as poor motion. Finally, the patients with four-part fractures had an acceptable functional outcome. Four-part fractures are a clinical challenge often leading to poor function and range of motion. Altogether, patients with three-part fractures showed better results in the scoring system, not statistically significant. Our patients with four-part fractures had no disability having been treated non-operatively, and all except one had severe osteoarthrosis at review. Furthermore, there was no increased satisfaction compared to the patients with the four-part fracture. Limitations of this study are that the study is retrospective and that there is a high dropout rate of the original series of 180 patients. The high dropout rate is a problem also seen in other studies, because most of our patients are geriatric patients (mean age 83.9 years in 4-part fractures); some of them were already dead. The others refused to come, were not registered, or could not be reached. Most of the elderly patients with proximal humerus fractures also have a lot of comorbidities, some of them with their joints with the consequence of walking disability. It seems to be a problem for them to appear for a clinical check-up.

A further limitation of the study was the diminished accuracy of fracture classification by standard radiographs when compared with CT-scan. However, all X-rays were checked by a second trauma consultant, an experienced shoulder surgeon, to ensure inter-observer reliability.

Nevertheless, the results from this study show a high patient satisfaction, despite low functional scoring and non-anatomical fracture reduction. This suggests that non-operative treatment of three- and four-part fractures of the proximal humerus, especially in elderly patients, should be considered as a treatment option.

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MENOPAUSE: THE IMPACT OF THE SEX HORMONE THERAPY ON THE HEALTH-RELATED QUALITY OF LIFE OF ELDERLY WOMEN

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ABSTRACT

The aim of this study is to evaluate and elucidate the outcomes of sex hormone treatment on the health of menopausal or postmenopausal women. Data were extracted from the literature through the MEDLINE database service for years 2004-09 using key words, 'hormone replacement therapy'. Hormone therapy (HT) devoting to clinical outcomes in the breast, ovary, endometrium, bone, cardiovascular system and brain, preferred use of synthetic steroids hormones to bio-identical steroids. Current data on oestrogen therapy (ET) suggested increased risks of venous thromboembolism and stroke. Prolonged use (>10 years) of ET was significantly associated with ovarian cancer in menopausal women. Women using oestrogen and testosterone therapy had high risk of breast cancer. Oestrogen-progestogen or oestrogen therapy-outcomes revealed no significant difference in ovarian or breast cancer risks. HT positively influenced climacteric depression by affecting neural activity and modulation of tones. Low dose of oestrogen-progestogen therapy suppressed endometrial proliferation resulting in amenorrhoea and relieved symptoms. Recent study had doubted the efficacy of HT to prevent cardiovascular diseases despite confirming the lipid lowering effect of oestrogen. Risks involved with HT might be reduced by using lower doses, bio-identical steroids, maintaining or eliminating progestogen, using non-oral-route in some women and initiating HT in symptomatic women near menopause. These studies have enriched our knowledge of risks-benefits associated with HT. Known benefits should be weighed against increased risks. This treatment should be individualised after carefully evaluating the conditions of the each elderly woman for relief.

INTRODUCTION

Menopause occurs naturally when the ovary ceases to produce follicles. This may be also produced artificially by surgical and / or medical ablation of the ovarian function. Menopause is a hypo -oestrogenic state, which may adversely affect oestrogen target tissues, such as brain, skeleton, skin,

cardiovascular, and genitourinary systems, with resultant frequency and severity of climacteric symptoms. For decades, hormonal replacement therapy (HRT) has been the mainstay and is being considered to be most effective for manageing menopausal symptoms. However, controversy has cropped up about the therapeutic benefit of this treatment after publication of results from the women's health Initiative study in July 2002. This controversy has in fact prompted to review the impact of HRT from time to time because elderly [menopausal or postmenopausal] women often need treatment to get relief from the menopausal or postmenopausal symptoms. In this article, an endeavour has been made to evaluate and elucidate various aspects of menopause and its symptoms along with the impact of HRT on the health related quality of life of the elderly women in the light of state of art of the modern treatment.

METHODOLOGY

A search was made for the literature using the key words, 'hormone replacement therapy' through the MEDLINE database service for years 2004-09. The articles, reviews, investigations, and studies pertinent to the theme were included for this review, which was composed traditionally to expose various aspects associated with menopause, related problems and HRT.

Menopause

Menopause is defined as the permanent cessation of menstruation[1]. An enduring puzzle in human life history is why women cease reproduction midway through life. The natural selection can favour post reproductive survival because older females can help their offspring to reproduce. However, gains for helping offspring appear insufficient to outweigh the potential benefit of continued reproduction. Why then do women cease reproduction in the first place? Here, Cant and Johnstone have opined that rapid senescence of the human female reproductive system coincides with the age at which, in natural fertile populations, women are expected to encounter reproductive competition from breeding females of the next generation. Several lines of evidences have suggested that in ancestral hominids, this younger generation typically comprises of immigrant females. In these circumstances, relentless asymmetries within families are predicted to give younger females a decisive advantage in reproductive conflict with older females. Therefore, a model incorporating both costs of reproductive completion and benefits of grand mothering can account for the timing of reproductive cessation in human females and thus, offers an improved understanding of the evolution of menopause [2].

Menopausal transition

The most common symptoms are hot flashes, night sweats, and irregular menstrual periods, loss of libido, vaginal dryness and mood swing, which may be experienced by women in their midlives. There may be other symptoms involving bone, brain, cardiovascular and / or neuromuscular systems affecting some menopausal or postmenopausal women. The symptoms of menopause usually last for the whole of menopausal transition, but some women may experience them for the rest of the lives.

Sex steroids act on the central nervous system both through genomic mechanism such as modulating synthesis, release and metabolism of many neuropeptides and through non-genomic mechanisms such as influencing electrical excitability, synaptic function, morphological features, and neuron-glia interaction. Deficiency of sex steroids causes many neuroendocrine changes during climacteric period. At the hypothalamic level, oestrogen withdrawal gave rise to vasomotor symptoms, eating behaviour disorders, and altered blood pressure control. However, at the limbic level, the changes in serotoninergic, noradrenergic and opiodergic tones contributed to the modification in mood and behaviour [3].

The menopausal transition involves a complex interaction of molecular and tissue-specific hormone receptors, enzymes, and moderating cofactors that determine the functional expression of a given organ. The synthesis and metabolism of oestrogen in oestrogen sensitive organs continue after menopause, but at levels substantially reduced from those of reproductive women. The postmenopausal production of oestrogen is genetically determined. Thus, symptoms of oestrogen deficiency may vary among menopausal women, although all women would cease menstruation [4]. Statistically significant gradients were seen between the ovarian venous and peripheral blood samples for testosterone (T), androstenedione, dehydroepiandrosterone (DHEA), oestrone (E_1), and oestradiol (E_2). The postmenopausal ovary was hormonally active, contributing significantly to the circulatory pool of T [5].

The reproductive ageing of women based on changes in menstrual cycle length and frequency progressed through various stages. Ovulatory cycle FSH, LH, and oestradiol levels increased and luteal phase progesterone decreased with progression through these stages. Early cycle inhibin B along with anti-Mullerian hormone decreased steadily across these stages and was largely undetectable during elongated cycles in the menopausal transition [6].

Both chronological and ovarian ageing of women in Michigan contributed to substantial changes in body composition, such as increase in fat-mass (3.4 kg), decrease in skeletal muscle (0.23 kg) and increase in waist circumference (5.7 cm) over six years at midlife. Waist circumference increased over the

time period, but the rate slowed down in one year after cessation of menstruation. The fat-mass continued to increase with no change in the rate. These changes have important ramifications for establishing a metabolic environment that could be healthy or unhealthy for women associated with these changes [7].

The body mass index (BMI) of premenopausal women aged 33–52 years in Boston was inversely associated with total oestradiol level and also with testosterone, androstenedione, and progesterone levels. Compared with women having BMI of ≥ 30 versus < 20 kg /m^2 levels were higher by 53 % for free testosterone and lower by 51 % for SHBG, 39 % for follicular oestradiol, 20 % for luteal oestradiol, 14 % for androstenedione, 13 % for testosterone and 20 % for progesterone (P). These findings suggested that effects on premenopausal sex hormone levels may he one mechanism through which adiposity affects premenopausal cancer risk [8].

The spine and hip bone mineral density (BMD) losses during the menopausal transition were found strongly related to the interaction between initial FSH levels and longitudinal FSH changes and not to E_2 or androgen levels or changes [9]. However, Schmitz and colleagues had identified a particular window of the menopausal transition during which physical activity was associated with reduced oestradiol and / or testosterone levels [10].

Factors associated with age at menopause

The life style of the woman is found to influence her age at menopause. A study in Norway suggested an association between current smoking and early menopause, which is defined as menopause occurring at an age of less than 45 years. The earlier a woman stopped smoking, the more protected she was from early menopause. However, no significant association was observed between early menopause and passive smoking, alcohol or coffee consumption, while high educational levels and high social participations of women had negative association with early menopause [11]. The risk of early menopause among Mexican women was also reported to have association with short menstrual cycles, a short period of oral contraceptive use, lower number of pregnancy, low BMI, low schooling levels, smoking history and birth cohorts [12].

The occupational factors influenced the age at natural menopause in gainfully employed French women (n=1,594). Among women with history of depression, a late menopause was associated with having at least one child and menarche later than the age of 13 years. Early menopause was associated with a high job control and high school education. Whereas, among women without such history, early menopause was associated with smoking (> 10 cigarettes /day), a high strenuous job and difficult schedules; while, late menopause was associated with higher educational status and repetitive work of women [13].

The findings of a study in Atlanta revealed that all-cause mortality rates were higher among women (non-smoker, having no HRT) who reported that natural menopause occurred at the age of 40–44 years as compared with women who experienced menopause at the age of 50–54 years. This increased risk was largely due to higher mortality rates from coronary heart disease, respiratory disease, genitourinary disease and external causes [14].

Early menopause in Caucasian women was reported to have association with increased risk of coronary heart di9sease. However, this association was also observed in menopausal Asian women. As compared with age at menopause of ≥ 49 years, those with age at menopause of < 49 years tended to have increased risk of coronary heart disease among women aged 40–44 years [15].

Health related quality of life

Many women have few or no symptoms at their natural menopause. These women are not in need of medical treatment. Premenopausal or post menopausal women who have menopause induced by surgery, chemotherapy or radiation are more likely to experience bothersome or even disabling symptoms. These women need safe and effective treatment. It is difficult to differentiate those symptoms that are truly associated with menopause from those due to ageing [16]. Among women at the age of 46–55 years (n=1206) in West Midlands, a positive association was observed between somatic and psychological dimensions of health related quality of life and participation in regular exercise. Women with BMI scores in normal range reported lower vasomotor symptoms scores and better health related quality of life scores than heavier women [17]. Mahabir and colleagues, in Houston, confirmed that women who were overweight or obese had significantly higher serum concentrations of E_2, bio-available E_2, oestrone, oestrone sulphate and lower SHBG than normal weight women [18]. These free oestrogen and low SHBG levels may have association with some ailments of menopausal or post menopausal women.

HRT associated risks-benefits ratio

Breast cancer

A cause-and –effect relationship between HRT and breast cancer still remains controversial. Recent study suggested that HRT users developed breast cancer at a younger age than nonusers. HRT use was associated with development of biologically more favourable cancer than those developed in nonusers as well as overall and disease free survival rate were higher in HRT users than nonusers [19]. However,

the increased risk of breast cancer associated with the use of oestrogen plus progestogen declined markedly soon after discontinuation of combined hormone therapy and was unrelated to the changes in frequency of memography [20]. A modest, albeit no significant elevation in breast cancer risk associated with E_2+T use was observed among postmenopausal women [21].

A positive association between obesity and postmenopausal breast cancer was attributed in part to the fact that oestrogen, a risk factor for breast cancer, was synthesized in the adipose tissue. Obesity was also associated with high level of insulin, a known mitogen. In a model that controlled for multiple breast cancer factors including E_2, and insulin level was associated with breast cancer only among nonusers of HRT. Obesity (BMI ≥30 kg/m^2) was also associated with the risk of breast cancer among nonusers of HRT. Thus, hyper insulinemia is an independent risk factor for breast cancer and may have a substantial role in explaining the obesity-breast cancer relationship [22]. No materially increased risk of breast cancer was observed in users of oestrogen alone or esterified oestrogen with methyl testosterone compared with nonusers, while an increased risk was noted among those using conjugated oestrogen and progestogen [23].

Among postmenopausal Finnish women, incidence ratio for all types of breast cancer was not elevated within the first 3 years of E_2+progestogen therapy but it rose to 1.31 for use from 3–5 years and to 2.07 with 10 or more years of use. Exposure to sequential progestogen for 5 years or more was accompanied with a lower risk elevation than exposure to continuous use. Oral or transdermal use of E_2+progestogen therapy was associated with comparable risk elevation for breast cancer. The use of norethisterone acetate was associated with higher risk after 5 years of use than that of medroxyprogesterone acetate. No excess risk of breast cancer with distance metastases was observed among E_2+ progestogen therapy users [24]. This shows oestradiol is better steroid than its synthetic counterpart in HRT.

Whether breast cancer risk varies by age and menopausal status? As compared to hormonal contraceptive method users among postmenopausal women aged less than 65 years, risk of breast cancer was moderately elevated for more than 5 years of HRT use. Among postmenopausal women aged 65 years or more, odds ratio for hormonal contraceptive method or HRT use was around null. These showed that timing of exogenous hormone use was important. Women who use that hormone before menopause had elevated risk, but these harmful effects began to decline with age after menopoause [25].

Women who consumed more than 25 g of alcohol per day had higher levels of oestrone, oestradiol, dehydroepiandrosterone sulphate and higher oestrone/oestradiol and oestrone/androstenedione ratios compared with non-drinkers. Thus, breast cancer risk increased with increased levels of alcohol consumption potentially through an effect on sex hormone levels. Therefore, the life-style of elderly women may also confound the increased risk of breast cancer among HRT users [26].

The risk of invasive breast cancer varied according to the progestogen component of combined postmenopausal hormone therapy compared with HRT never use. Ever use of E_2+P was not significantly associated with the risk of any breast cancer subtype but increasing duration of E_2+P was associated with a significant increase in risk of lobular carcinoma. E_2+other progestogen were associated with significant increase in risk of ductal and lobular breast cancer [27].

Ovarian cancer

Oral hormone therapy was associated with risk of ovarian cancer in elderly women with intact uteri. This risk increased with cumulative oral E_2 intake but not with duration of therapy indicating that increased risk of ovarian cancer associated with menopausal hormone therapy might be diminished substantially by minimising the daily dose of E_2 from oral hormone therapy [28]. Use of unopposed E_2 for fewer than 10 years was not associated with ovarian cancer. Compared with use of HRT, use of unopposed E_2 for 10 or more years was significantly associated with ovarian carcinoma in women (n=93,638) aged 50–71 years but not significant among women with hysterectomy. Compared with non-use of HRT, use of sequential (<15 days / cycle) or continuous (>15 days /cycle) E_2+progestogen for 5 or more years was significantly associated with ovarian cancer [29]. The increased risk in E_2 therapy users was statistically significantly higher than the risk in E_2+progestogen users. E_2 therapy increased risk of ovarian cancer in a duration-dependent manner. It appeared that addition of progestogen blocked this effect, at least to some extent [30].

As compared with normal weight women (BMI =18.5–24.9 kg / m^2), the relative risk of ovarian cancer for obese women (BMI ≥ 30 kg / m^2) in the cohort was 1.26. Among women who never used menopausal hormone therapy, the relative risk for obese versus normal weight women was 1.83. However, no relation between BMI and ovarian cancer was apparent among women who ever used HRT. These findings suggested association of obesity with enhanced ovarian cancer risk through hormonal mechanism [31].

Various studies showed that risk of ovarian cancer increased 1.28-fold by E_2 therapy and 1.11-fold by E_2+progestogen therapy. The risks were shown greater in European than North American studies for both E_2 and E_2+progestogen therapy. Given the widespread use of hormone therapy, known benefits should be weighed against the increased risks of ovarian cancer [32].

Endometrial cancer

A long-term use of unopposed oestrogen was associated with increased risk for endometrial cancer among postmenopausal women, whereas combined oestrogen–progestogen hormone therapy was not. Thus, if HRT be used in women with an intact uterus, this finding confirmed the benefit of adding progestogen to the regimens [33]. Magyar and Colleagues in Hungary opined that continuous oestrogen-progestogen therapy started at the right time even before menopause might reduce chance of development of endometrial hyperplasia. Hormonal treatment did not pose a risk for the development of endometrial carcinoma. On the contrary, continuous combined therapy appeared to reduce the risk of hyperplasia and indirectly, the chance of development of adenocarcinoma [34].

Colorectal cancer

Evaluation of colorectal cancer risk associated with HRT among postmenopausal women (n=56,733) showed a decreased risk of colorectal cancer among ever users of unopposed oestrogen therapy. The largest reduced risk was observed for current oestrogen users and users of ≥10 year duration. The reduced risk was also found among users of oestrogen plus progestogen therapy with sequential regimen users (progestogen <15 days / cycle) having the largest risk reduction. The past users of ≥5 years had the largest risk reduction [35]. However, a study in New York suggested that endogenous oestrone was associated with increased risk of colorectal cancer in postmenopausal women [36]. The postmenopausal HRT lowered colon cancer incidence in women. The mechanism is unknown, but animal models suggested that chemo preventive action of HRT on colon neoplasia resulted, at least in part, from changes in Vitamin D activity [37].

Vascular diseases

Oral but not transdermal oestrogen therapy was associated with an increased risk of venous thromboembolism (VTE) in postmenopausal women. Norpregnane derivatives might be thrombembolic, whereas micronized progesterone and norpregnane derivatives appeared safe with respect to VTE risk [38]. More consistent data were available reporting an increased risk in the incidence of VTE and stroke among postmenopausal women using oestrogen therapy [39]. The risk of VTE in women using oral oestrogen was higher in the first year of treatment compared with treatment for more than one year. No noticeable difference in the risk of VTE was observed between unopposed and opposed oral oestrogen treatment. However, increased risk of VTE among women using oestrogen therapy was confirmed. The combination of oral oestrogen and thrombogenic mutation or obesity further enhanced the risk of VTE, whereas transdermal oestrogen did not confer additional risk in women at high risk of VTE [40]. However, the risk for women with prothrombotic mutation using transdermal oestrogen was similar to that of women with a mutation who were not using oestrogen [41].

Cardiovascular disease (CVD)

Women who initiated HRT closer to menopause tended to have reduced coronary heart disease (CHD) risk as compared with the increase in CHD risk among women more distant from menopause [42]. The severity of coronary artery disease (CAD) in women might be influenced by the common ER-alpha polymorphism. This association was independent of other risk factors for CAD [43]. Women with a hysterectomy exhibited more CVD than those with an intact uterus. As compared to oestrogen-progestogen therapy oestrogen only therapy was significantly lower for myocardial infarction and breast cancer and higher for colon cancer. These findings confirmed that post menopausal women in the overall population responded differently to oestrogen-only treatment as compared with oestrogen-progestogen treatment, due to different hormone regimens and / or increased CVD in hysterectomized women [44]. The cardiovascular benefits of natural oestrogen supplementation on vascular endothelial function might be dependent on postmenopausal age with improved vascular function evidently only in the early postmenopausal years [45].

In postmenopausal women without CAD, the intra coronary oestrogen infusion mediated a greater increase in coronary blood flow and was positively correlated with the reduction of the coronary sinus endothelin-I levels at the peak of atrial spacing [46]. Studies suggested that oestrogen or oestrogen-progestogen therapy significantly reduced the risk of CHD in postmenopausal women; however the women Health Initiative Study (WHI) showed contrary findings. Koh and Sakuma focused on this controversial effect of oestrogen and oestrogen-progestogen therapy on cardiovascular system and suggested a hypothesis that the failure of oestrogen and oestrogen-progestogen therapy in reducing the risk of cardiovascular events in post menopausal women might be because of the stage of their atherosclerosis at the time of initiation of those therapies [47].

CNS and brain function

Whether HRT in menopausal women affects regional brain volume? The study showed that conjugated equine oestrogen (CEE) with or without MPA were associated with greater brain atrophy among women aged 65 years and older. However, the adverse effects were most evident in women experiencing cognitive deficits before initiating HRT [48]. Coker and colleagues claimed that CEE based HRT was not associated with a significant increase in ischemic brain lesion volume relative

to placebo control. This finding was consistent within each trial and in pooled analysis across trials [49]. Currently, HRT or ERT for cognitive improvement or maintenance was not indicated for women with Alzheimer's disease or other dementia syndromes [50].

Oestrogen plus progesterone therapy was more effective than oestrogen alone in decreasing the prevalence of periodic limb movement and hot flashes at night, or somnolence and attention difficulty during the day in Brazilian postmenopausal women. The prevalence of breathing irregularities, arousal from sleep, anxiety and memory impairment were decreased in both E_2 treated and control groups following progesterone treatment [51]. A recent report advocated for treatment of menopausal vasomotor instability, a novel transdermal oestradiol spray that delivers low dose oestradiol directly into the subcutaneous microcirculation with minimal skin reaction. There was a significant decrease in hot flash frequency and intensity as compared with control group, thereby indicating the use-effectiveness of low dose oestradiol over the synthetic oestrogen for treatment of elderly women [52].

Use of bio-identical hormones

The use of bio-identical hormones such a progesterone, oestradiol and estriol in HRT has sparked debate. Physiological data and clinical outcomes demonstrated that bio-identical hormones were associated with lower risk including the risk of breast cancer and cardiovascular disease and were more efficacious than their synthetic and animal derived counterparts. Until evidence is found to the contrary, bio-identical hormone appears to be the preferred method of HRT. However, further randomised controlled trials are needed to delineate these difference more clearly [53].

CONCLUSION

In spite of controversy about the therapeutic benefits of the HRT, this therapy is still considered to be the effective approach for managing menopausal syndromes, however, with reduction of doses of steroids, altering the route of administration and using bio-identical steroids in the HRT to reduce the risk of adverse effects. Moreover, hormone therapy should be individualised on carefully considering the need, exigency and condition of the each elderly women for alleviating their problems to improve upon the health related quality of life.

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CONTRIBUTION OF DUAL-FREQUENCY BIOIMPEDANCE SPECTROSCOPY TO EVALUATION OF DRY WEIGHT IN CHRONIC HAEMODIALYSIS PATIENTS

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ABSTRACT

The cardiovascular morbidity and mortality of chronic haemodialysis patients is markedly influenced by fluid status. We evaluated the possibilities of dual-frequency bioimpedance spectroscopy to assess the fluid status and specification of dry weight. We examined fifty-seven patients, who were included in the chronic haemodialysis programme at our workplace. Measuring was repeatedly performed after the haemodialysis session. A dual-frequency bioimpedance spectroscopy (DBIA) analyser (Inbody 230, Biospace Co. Ltd, Seoul, Korea) was used to measure body composition, i.e. fat, lean mass and total body water content. The median of difference between measuring was 0.37 % of total body water (TBW). All patients were clinically and radiologically examined before the haemodialysis; blood pressure values were monitored. The patients were divided into normovolemic and hypervolemic. The first subgroup of 31 normovolemic patients with arterial pressure under 140/90 and the second subgroup of 26 clinically or radiologically hypervolemic and all hypertensive patients were compared by DBIA against each other. We used the Student's t-test for sets with different variability. A highly significant difference ($p < 0.001$) in body water fraction (TBW/body weight) was detected. The median of TBW/BW in normovolemic and hypervolemic patients was 48.1 % and 61.1 % respectively. Later we considered TBW/BW in various BMI subgroups and found the same results. We commend its use to specify dry weight, particularly in hypertensive patients and patients with frequent intradialytic hypotension.

ABBREVIATIONS USED

TBW – total body water
TBW/BW – total body water divided by body weight
DBIA – dual-frequency bioimpedance spectroscopy analysis

BMI – body mass index
ESRD – end-stage renal disease
UF – ultrafiltration
HD – haemodialysis

INTRODUCTION

End-stage renal disease (ESRD) patients treated with intermittent haemodialysis retain water and salt between haemodialysis sessions. Fluid removal to achieve fluid balance is an important part of haemodialysis. Ultrafiltration prevents progressive fluid accumulation, development of oedema, hypertension, and heart failure. In clinical dialysis it is essential to define dry weight for each patient. Largely, dry weight is clinically determined and usually reflects the lowest weight that a patient can tolerate without intradialytic symptoms and hypotension in the absence of overt fluid overload. Both under- and overhydration in dialysed patients are associated with harmful consequences. Despite considerable advances in the assessment of dialysis adequacy, there is at present no exact measurement of adequacy for fluid removal. It is difficult to determine whether an individual patient is over- or underhydrated. It is well known that intradialytic complications are influenced by the balance between ultrafiltration rate and plasma refilling rate. UF rates in excess of plasma refilling capacity leads to dialysis-induced hypotension. It is evident that more exact methods of determining volume changes during HD are required for assessment of the goal for fluid removal. Therefore, we decided to evaluate the contribution of DBIA to specify the assessment of dry weight in ESRD patients. Bioimpedance describes the response of a living organism to an externally applied electric current. It is a measure of the opposition to the flow of that electric current through the tissues, the opposite of electrical conductivity. The measurement of the bioimpedance of humans has proved useful as a non-invasive method for measuring body composition (known as bioelectrical impedance analysis or simply BIA).

MATERIALS AND METHODS

The study was carried out with 57 patients placed in a chronic haemodialysis programme (32 males and 25 females). All patients were able to undergo DBIA examination. Physicians evaluated the fluid status (excluded were oedemas and signs of heart failure). Chess x-ray examination was performed in each patient, and the signs of hyperaemia were evaluated – hyperaemia of hilus, fluidothorax, or dilatation of heart shadow. Blood pressure was monitored in nondialysis days by an Omron M6 Comfort digital tonometer. The patients were instructed to measure their blood pressure in sitting position after 10 minutes of rest. Three values were gained and the second and third values were calculated to average. The patients monitored their blood pressure three times a day: in the morning, noon, and evening. The averages were calculated to final one average value. The value of 140/90 mm Hg was selected as the border between normo- and hypervolemic subjects. The patients underwent DBIA 30 minutes after haemodialysis; the measurements were repeated to exclude error. The median of differences between two subsequent measurements was 0.37 % TBW/BW.
A DBIA analyser, Inbody 230, Biospace Co. Ltd, Seoul, Korea, was used. DBIA accuracy was compared (by producer) with dual x-ray densitometry with an extremely tight correlation index of 0.974. According to the clinical assessment, x-ray examination and mean value of blood pressure, the patients were divided into two subgroups – first, normovolemic, and second, hypervolemic. The values of TBW/BW were evaluated by the Student's t-test for sets with different variability.

RESULTS

A significant difference ($p = 0.001$) of TBW/BW was found between normovolemic and hypervolemic patients. The TBW/BW median of 31 normovolemic patients was 50.4 %, standard deviation 8.5 %, the TBW/BW median of 26 hypervolemic patients was 58.2 %, standard deviation 9.0 %. In the subgroup of patients with BMI less than 25 the TBW/BW median of 12 normovolemic patients and 14 hypervolemic patients was 57.4 % and 62.4 % respectively; standard deviation for normovolemic and hypervolemic patients was 6.9 % and 7.4 % respectively (statistically significant difference, $p=0.04$). In the subgroup of patients with BMI between 25–30 the TBW/BW median of 9 normovolemic patients and 7 hypervolemic patients was 48.9 % and 58.8 % respectively; standard deviation for normovolemic and hypervolemic patients was 3.4 % and 6.1 % respectively (statistically highly significant difference, $p=0.003$). And finally in the subgroup of patients with BMI higher than 30 the TBW/BW median of 10 normovolemic patients and 5 hypervolemic patients was 40.9 % and 46.7 % respectively; standard deviation for normovolemic and hypervolemic patients was 6.9 % and 5.5 % respectively (statistically non-significant difference, $p=0.21$). Mean diuresis in normovolemic and hypervolemic patients was 625 ml and 1300 ml per day respectively (statistically non-significant difference), the average consumption of antihypertensive drugs was in normovolemic and hypervolemic patients 3.8 and 4.7 respectively (statistically non-significant difference). Older subjects were prone to hyperhydration, the median of age of normovolemic patients was 66 years and 70 years in hypervolemic patients. The mean predialysis blood pressure did not correlate with the fluid status; no statistically significant difference was found.

CONCLUSION

We cannot commend clear digits of TWB/BW; however, on the basis of the difference of a particular patient's TBW/BW value and the median TBW/BW value in the proper BMI subgroup, we can estimate the fluid status. The study detected 11 patients with silent hypervolemia and 4 chronic hypovolemic patients. Higher predialysis blood pressure values in hypervolemic patients were not confirmed, in spite of this well-known and respected fact. We suppose that transport of patients to the HD unit distorted the measuring of predialysis blood pressure. Due to the low ratio of patients with BMI over 30, we did not confirm statistically significant difference for TBW/BW. Dry weight is a dynamic value, therefore repeated measurements are warmly supported. Clinical assessment of the patient's fluid status alone is unsatisfactory.

DISCUSSION

DBIA is a simple, non-invasive, highly reproducible, and accurate method for monitoring body composition. The principal issue of DBIA is interpretation. When using the BIA method, physicians should perform so as to increase the accuracy of determining dry weight. We commend its use to specify dry weight, particularly in hypertensive patients and patients with frequent intradialytic hypotension.

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