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Chapter 29

PARKINSON'S DISEASE AND INTERMITTENT HYPOXIA TRAINING

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ABSTRACT

The disturbances of central and peripheral catecholamines (CA) metabolism, mainly dopamine (DA), are a basis of Parkinson's disease (PD) development. CA also take part in breathing regulation as transmitters and modulators of peripheral chemoreceptors and are involved in breathing rhythmogenesis. Last decades the classical triad of PD symptoms – akinesia, rigidity and muscle tremor - has been supplemented by respiratory disorders. The rearrangement of respiratory function in PD are determined by specific activity of the neuro-muscular apparatus which provide lung ventilation and also by the specific neurochemical respiratory control. In this chapter, we describe the peculiarities of ventilatory responses to main respiratory stimuli – O_2 and CO_2 in PD patients. We also describe fundamental theoretical and practical Intermittent Hypoxia Training/Treatment (IHT) principles that allow to use this method for clinical therapy of PD. The results of the examination of healthy elderly people, non-treated and L-DOPA-treated PD patients before and after 14-days course of IHT are discussed. After IHT, a significant rise in hypoxic ventilatory response (HVR) was observed both in healthy people and PD patients without any changes in hypercapnic ventilatory response (HCVR). IHT was accompanied by a more intensive CA turnover, in particular, dopamine synthesis, as compared to the sham-treated patients. We hypothesize an improvement of neuromuscular and respiratory control in Parkinsonian patients under IHT, which may be related to the positive shifts in dopamine and CA metabolism.

INTRODUCTION

It is widely recognized that Parkinson's disease (PD) is a disorder based on the degenerative changes in pigment-containing nuclei of brain stem - *substantia nigra (SN)* and *locus coeruleus (LC)* [Ehringer & Hornykiewicz, 1960; Veyn & Golubev, 1981]. More specific biochemical peculiarities of PD are insufficient synthesis of dopamine (DA) in basal ganglions and an imbalance in DOPA-deficient neuromediator [Ehringer & Hornykiewicz, 1960; Hornykiewicz, 1988]. The clinical symptoms of PD develop following the loss of 70% of DA in the striatum. Yet James Parkinson noted that his patients "fetched their breath rather hard". So, the classical triad of PD symptoms – akinesia, rigidity and muscle tremor - has been supplemented by respiratory disorders.

THE STATE OF RESPIRATORY MECHANICAL APPARATUS IN PD

All series of studies have provided evidence of the significant changes in the functioning of mechanical apparatus of breathing in PD patients, which become more severe as the disease develops.

The rigidity and muscle bradykinesia that are distinctive of PD hinder rapid repetitive respiratory motions; moreover, the pathological processes affect the muscles of upper respiratory pathways leaving the function of diaphragma in relative "inviolability" [Vincken et al., 1984; Tzelepis et al., 1988; Izquiredo-Alonso et al., 1994; Cardoso & Pereira, 2002; Sathyaprabha et al., 2005]. Protracted inspiratory EMG muscle activity during expiration [Estenne et al., 1984] and the duration of the respiratory cycle [Bellemare et al., 1982] are apparent in PD. A decrease in the forced vital capacity (FVC), total lung capacity (TLC), maximal lung ventilation (MLV), forced expiratory volume per 1 sec (FEV_1), Tiffeneau index (FEV_1%VC) and an increase in residual volume (RV) and total resistance of respiratory pathways (R_{rs}) [Neu et al., 1967; Yadgarov & Nikolaenko, 1971; McIntosh, 1977; De Keyser & Vicken, 1985; Izquiredo-Alonso et al., 1994; Sabate et al., 1996a, 1996b; Serebrovskaya et al., 1998] indicate the functional limitations of respiratory mechanical apparatus. At the same time, there have been reports about the preservation of VC, FEV_1%VC [Hovestadt et al., 1989], FEV_1 [Serebrovskaya et al., 2003] and the obturation of respiratory pathways only on a subclinical level in a significant number of Parkinsonian patients**.** Overall though there are shifts in the functioning of respiratory mechanical apparatus per se, the intensity of which increases as PD progresses. At the same time, it is possible that the rearrangement of respiratory function in PD is determined not only by the specific activity of neuro-muscular apparatus which provide lung ventilation, but also by the neurochemistry of respiratory control.

LUNG VENTILATION IN PD

The changes in time-volume parameters of lung ventilation are considered to be a specific peculiarity of PD [Neu et al., 1967]. The breathing of PD patients is characterised by a higher respiratory rate than in healthy persons [Yadgarov & Nikolaenko, 1971; Apps et al.,

1985; Brown, 1994; Kolesnikova, 2001; Serebrovskaya et al., 2003]. However, the absence of measurements of minute expiratory volume (V_E) and partial tension of CO_2 in the arterial blood ($PaCO_2$) in some studies makes it difficult to determine the cause of tachypnea: is this phenomenon a manifestation of hyperventilation or the result of the rearrangement of respiratory pattern due to other factors [Brown, 1994]. Yadgarov and Nikolaenko [1971] observed an increased V_E in PD patients (by an average of 41%) accompanied by a non-significant increase in alveolar ventilation. According to the data of Apps et al. [1985], tachypnea in PD exists against a background of normal haemoglobin saturation without any signs of hyperventilation. At the same time, in separate studies [Noe et al., 1967; McIntosh, 1977; Sabate et al., 1996a, 1996b], tachypnea was accompanied by decreased oxygen saturation of arterial blood (SaO_2) and lowered O_2 partial tension in the blood (PaO_2), which in some cases co-existed with hypoventilation [McIntosh, 1977]. Sabate et al. [1996a, 1996b] recorded PaO_2 and $PaCO_2$ below the normal value. However, in the opinion of Neu et al. [1967], hypoventilation is not a typical component of the PD syndrome. In our own examinations [Kolesnikova, 2001; Serebrovskaya et al., 2003] V_E as well as O_2 and CO_2 alveolar partial pressure (P_AO_2 and P_ACO_2) in patients with PD were no different from the control values of healthy people of the same age, which allowed us to reach a conclusion about the changes in respiratory pattern against a background of the absence of significant signs of hypo- or hyperventilation. Furthermore, according to our own research tachypnea is more common in patients treated by L-DOPA [Kolesnikova, 2001; Serebrovskaya et al, 2003].

Irregular character of breathing pattern is attributed to more specific shifts in the breathing “picture” [De Keyser & Vincken, 1985]. In PD, the breathing pattern may become arrhythmic [Yadgarov & Nikolaenko, 1971; Weiner et al., 1979] with increased variation in amplitude while in other cases, there is a curious uniformity in respiratory rate and depth [McIntosh, 1977]. The causes of such changes in breathing pattern have not been established.

VENTILATORY RESPONSES TO HYPOXIA AND HYPERCAPNIA (HVR, HCVR) IN PD PATIENTS

The sensitivity of respiratory system to main chemical stimuli – O_2 and CO_2 – is an important component of the mechanism of homeostasis. PD is accompanied by essential changes in HVR and HCVR. Some authors have noted the tendency for a rise in HVR in patients with PD [Rosen et al., 1985; Feinsilver et al., 1986]. However, according to our own observations, PD is characterised by a decrease in HVR [Serebrovskaya et al., 1998; Kolesnikova, 2001; Serebrovskaya et al., 2003] (Figure 1). Rosen et al. [1985] and Feinsilver et al. [1986] found significantly increased HCVR in PD. In contrast, Yadgarov and Nikolaenko [1971] found a clear reduction in HCVR. Our research has provided evidence of the preservation of HCVR in PD patients [Kolesnikova, 2001; Serebrovskaya et al., 2003] (Figure 2). Similar results were reported by Onodera et al. [2000].

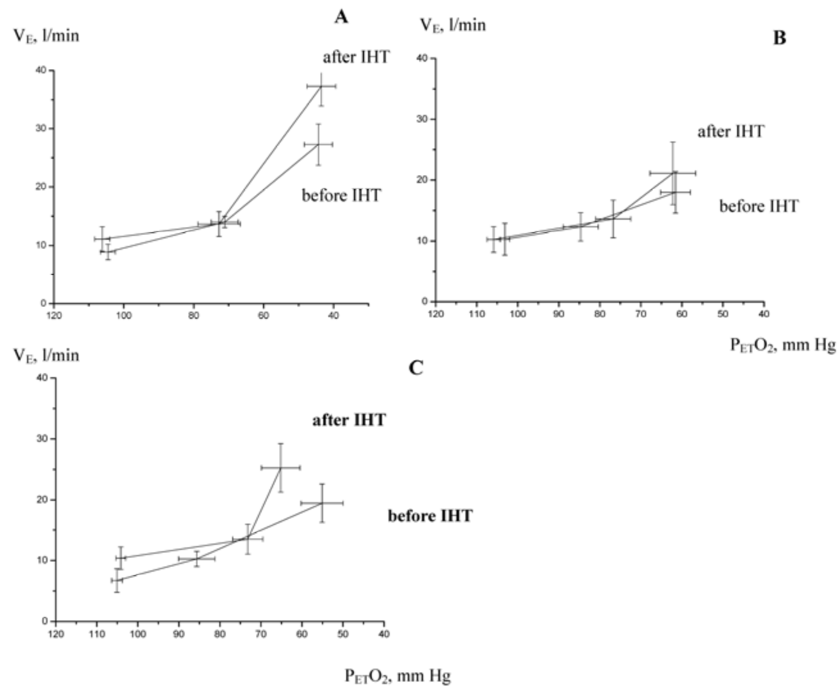

Figure 1. Hypoxic ventilatory responses to isocapnic progressive hypoxia in healthy elderly persons (A), non-treated (B) and L-DOPA-treated (C) patients with Parkinson's disease before and after intermittent hypoxic training (IHT).V_E - expired minute ventilation; $P_{ET}O_2$ - end-tidal PO_2. The dependence between V_E and $P_{ET}O_2$ was analyzed by the technique of piecewise linear approximation [Serebrovskaya & Vergulis, 1985; Serebrovskaya, 1992].

POSSIBLE CAUSES OF HVR AND HCVR ALTERATIONS IN PD

Interpretation of the observed changes in HVR and HCVR in PD patients is of great interest. Rosen et al. [1985] linked the phenomenon of relative rise in HVR and HCVR with DA deficiency in the central nervous system (including central pattern generator, CPG), suggesting an inhibitory effect of CA on respiratory drive. The HCVR reduction can be determined by the rigidity of chest wall and the lack of mechanical realisation of "commands" from CPG without changes in the sensitivity of central chemoreceptors to CO_2 [Yadgarov & Nikolaenko, 1971].

It is logical to examine the potential relationships between a decrease in HVR [Serebrovskaya et al., 1998; Kolesnikova, 2001; Serebrovskaya et al., 2003] and limited possibilities for muscular apparatus to develop significant ventilation in PD. Special attention is given to the data on a decrease in HVR under myopathy, which is characterised by muscle weakness [Wilson et al., 1987]. However, the studies of Canning et al. [1997] and Serebrovskaya et al. [2003] suggest that a decrease in HVR may be determined not only by disorders in the muscle apparatus function but also in the alterations in respiratory control, since Parkinsonian patients are able to develop an almost normal level of arbitrary ventilation for a short period. It is well known that the neurochemical basis of PD is mainly related to the

breach in DA metabolism [Ehringer & Hornykiewicz, 1960]. DA release from the chemoreceptor cells of carotid bodies (CB) is an important parameter of the chemoreceptor function, which is closely related to the degree of hypoxia and the activity of carotid sinus nerve which transfers afferent impulses into CPG [Gonzalez et al., 1994]. In PD there may be alterations in the chemoreception of O_2 related to DA metabolism. The same decrease in respiratory sensitivity to O_2 was noted in response to reduced thyroid gland function (i.e. hypothyroidism) [Ladenson et al., 1988]. The characteristic symptom of hypothyroidism is the deficiency of initial products for the synthesis of thyroid hormones - phenylalanine and thyrosine, which are the precursors for CA and DA synthesis in the chain of biochemical transformation.

In our study, a lower HVR in non-treated PD patients and an increased HVR in L-DOPA-treated patients (Figure 1) are consistent with our hypothesis about a general disorder in DA metabolism that affects CB function [Serebrovskaya et al., 1998; Kolesnikova, 2001; Serebrovskaya et al., 2003]. L-DOPA probably enhances the increase in HVR if DA is an excitatory transmitter in the CB [Gonzalez et al., 1994], and the main effect of this agent is realised at the CB level [Bianchi et al., 1995]. At the same time, the HVR of L-DOPA-treated PD patients was lower than in healthy people, and was accompanied by the highest level of blood DA (Figure 3) [Kolesnikova, 2001; Serebrovskaya et al., 2003]. The possibility of an inhibitory modulatory effect of DA in the circulation on the peripheral mechanisms of breathing regulation (which are central to HVR formation) is completely consistent with the results of Bascom et al. [1991] and Ide et al. [1995].

The results of our HCVR examination in Parkinsonian patients also support the "neurochemical hypothesis", which explains the shifts in respiratory function in PD. Obviously HCVR depends on the CA metabolism to a lesser degree than HVR. It is known that HCVR formation relates to the activity of central chemoreceptors and, only partially (about 20%) to the activity of the CB. We observed a rise in respiratory reaction to CO_2 just at the initial stage of HCVR only in L-DOPA-treated patients [Kolesnikova, 2001]. Differences in subsequent evolution of the HCVR curve in Parkinsonian patients and healthy people were not found [Kolesnikova, 2001]. It is likely that the absence of differences in HCVR indicates a lesser degree of injury at the *central* link of the mechanism of breathing regulation vs. its *peripheral* site.

The ability of PD patients to demonstrate normal values of HCVR allows us to conclude that the limitation of muscle function of ventilatory apparatus is not always the main factor in the rearrangement of respiratory control in PD. Analysis of the results from different studies suggests that the "mechanical" and/or "neurochemical" factors of respiratory control and breathing regulation correspondingly correlate with the stage, clinical form and pharmacological compensation of PD.

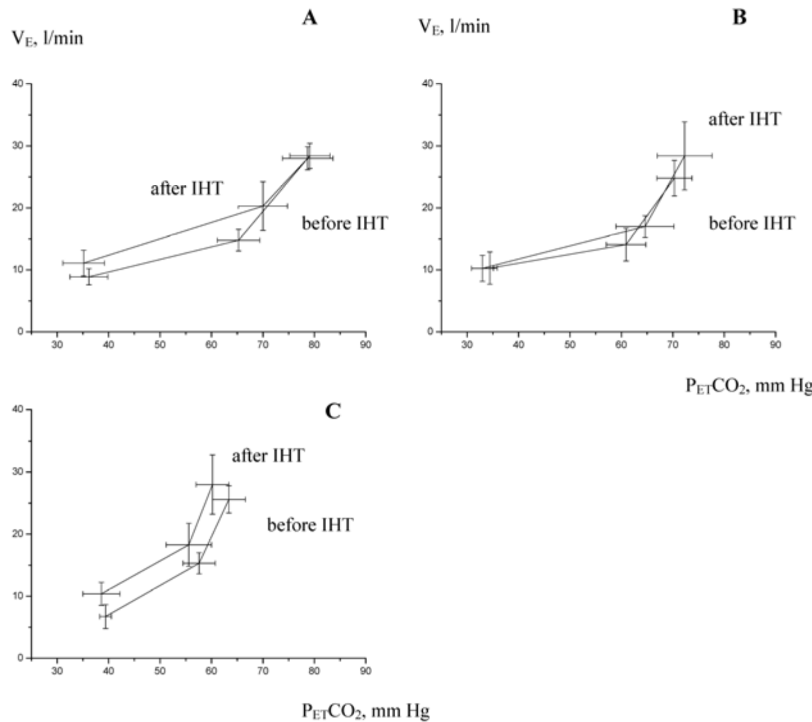

Figure 2. Hypercapnic ventilatory responses in healthy elderly persons (A), non-treated (B) and L-DOPA-treated (C) patients with Parkinson's disease before and after intermittent hypoxic training (IHT).V_E - expired minute ventilation; $P_{ET}CO_2$ - end-tidal PCO_2. The dependence between V_E and $P_{ET}CO_2$ was analyzed by the technique of piecewise linear approximation [Serebrovskaya & Vergulis, 1985; Serebrovskaya, 1992].

INTERMITTENT HYPOXIC TRAINING (IHT)

The conception of positive effects of IHT on human organism is an exceptional prerogative of Ukrainian and Russian scientists [Serebrovskaya, 2002]. It is well-known that adaptation to IHT leads to an increase in the respiratory sensitivity to a hypoxic stimulus, reinforces haemopoiesis and activates the sympatho-adrenal system [Engwall & Bisgard, 1990; Reeves et al., 1992; Serebrovskaya & Ivashkevich, 1992; Bisgard, 1995; Aaron & Powell, 1993; Reeves et al., 1996; Asano et al., 1997; Serebrovskaya et al., 1999; Bernardi et al., 2001; Kolesnikova, 2002]. Furthermore, the basic rate-limiting enzyme for CA synthesis – tyrosine hydroxylase (TH) is an oxygen-dependent enzyme that is activated following a PO_2 drop [Czyzyk-Krzeska et al., 1992]. In addition, adaptation to hypoxia is accompanied by an increase in DA content in chromaffine cells of the CB [Bee & Pallot, 1995].

We supposed that adaptation to IHT could assist with the normalisation of respiratory parameters in patients with PD by improving DA metabolism. To confirm this statement, we examined healthy elderly persons and patients with PD (non-treated and treated with L-DOPA - levodopa/carbidopa, 100-250 mg/day) during a 14-day course of IHT. Patients had signs of disease that corresponded to the 1.5-2.5 degree according to the Unified Parkinson

Disease Scale (UPDRS). Hypoxic episodes were created by continuous breathing of subjects into a closed spirograph with dosed CO_2 absorption [for details see: Kolesnikova, 2002; Serebrovskaya et al., 2003]. Continuous rebreathing was performed for 5 to 6 min; this resulted in a drop in the O_2 content in inspired air down to 7-8%. The period of severe hypoxia (F_IO_2 from 10 to 7%) lasted no more than 1.5 minutes. Such a mode evoked no considerable negative subjective sensations in the tested persons. Over the IHT course, hypoxic sessions were repeated three times a day.

EFFECTS OF IHT ON PD

A 14-day course of IHT did not lead to significant changes in lung ventilation in healthy elderly persons or patients with PD. After the IHT course we observed more significant shifts in HVR vs. HCVR [Kolesnikova, 2001; Serebrovskaya et al., 2003] (Figure 1). The demonstrated increase in HVR after IHT in all examined persons was compared with results related to high altitude adaptation [Engwall & Bisgard, 1990; Aaron & Powell, 1993]. HVR increased in healthy people by about 75% ($p<0.05$) (Figure 1). However, more prominent changes in HVR (2-fold increase) were observed in the L-DOPA-treated patients, moving them nearer to the values from healthy people. The rise in HVR in the non-treated patients was by 52% ($p<0.05$). HCVR did not change in any examined person after IHT (Figure 2).

The shifts in respiratory control following adaptation to IHT were realized against a background of certain changes in the metabolism of DA and its precursor DOPA (Figure 3). It is well-known that adaptation to hypoxia is accompanied by the activation of the sympatho-adrenal system and by a corresponding increase in CA levels in biological liquids [Reeves et al., 1996; Asano et al., 1997]. At the same time, we observed a decreased blood DOPA and blood DA content in healthy people and PD patients. TH activity (converts tyrosine into DOPA) and the activity of DOPA-decarboxylase and DA-β-decarboxylase (catalyses the conversion of DOPA into DA, and DA into norepinephrine, respectively) decrease with age [Gey et al., 1965; Green, 1974; Ponzio et al., 1978]. After IHT in elderly people blood DOPA levels decreased but blood DA content was unchanged (Figure 3). In PD patients, blood DOPA and blood DA were lowered after IHT. Obviously, after IHT the main changes in catecholamine synthesis in healthy elderly people and PD patients could be realized owing to more significant DOPA-decarboxylase activation (as the result there was a decreased blood DOPA) vs. TH activation in young persons. At the same time, it is necessary to note that the reserves for enzymatic CA synthesis are limited, although they are increased under the influence of IHT.

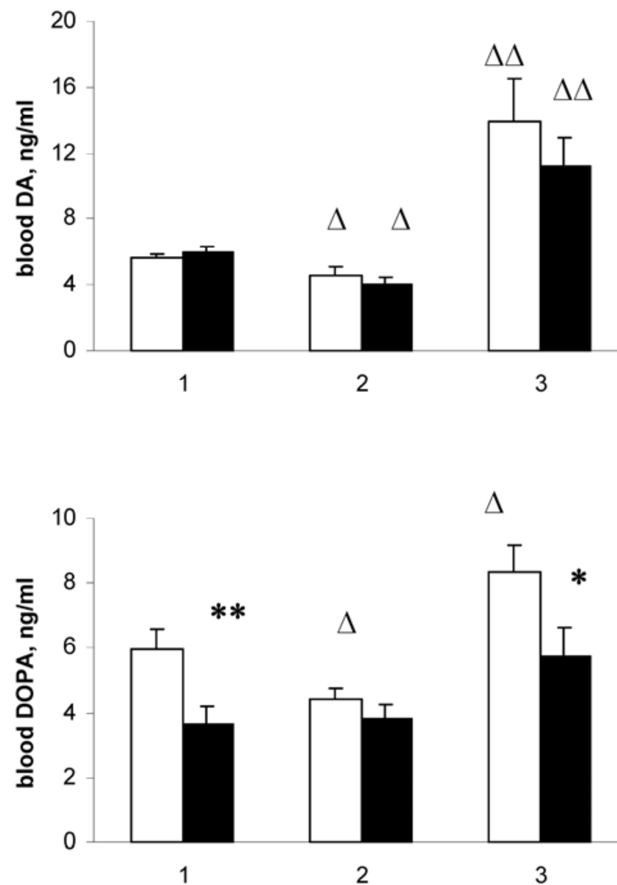

Figure 3. Blood dopamine (DA) and DOPA level in healthy elderly persons (1), non-treated (2) and L-DOPA-treated (3) patients with Parkinson's disease before (white column) and after (black column) IHT course. The difference before and after IHT: ∗ $p<0.05$; ∗∗ $p<0.01$. The difference between healthy persons and patients with Parkinson's disease: Δ $p<0.05$; ΔΔ $p<0.01$.

The comparison of HVR and DA metabolism parameters suggests that the rise in HVR in healthy people as well as in PD patients is related to the alteration in respiratory control and neuromuscular regulation. The changes in HVR and CA metabolism were accompanied by positive clinical dynamics in PD patients – the improvement of EMG, diminution or disappearance of muscle tremor, the increase of motor temp.

According to current physiological notions, adaptation to hypoxia leads to an increase in DA content in the CB [Bee & Pallot, 1995] and modulates CA levels in the brain stem areas that are related to respiratory control [Soulier et al., 1997]. It is likely that these processes contain the basis for the HVR rise under IHT adaptation. According to our results, more changes in HVR and intensive DA production were observed in healthy elderly people. At the same time, PD patients demonstrated lowered stimulation of CA synthesis that determined the reduced HVR values even under L-DOPA treatment (Figure 1).

Besides this, the rise in HVR in patients with PD during IHT adaptation could be determined by the increase in DA content in the striatum and the corresponding improvement

of neuromuscular control as a whole, and in particular, the control of the respiratory muscles. This assumption is based on the studies of rats with experimental DA insufficiency that were exposed to the same course of IHT [Belikova et al., 2007]. A significant increase in DA content in the striatum of experimental animals after the IHT course was observed. The mechanism of positive IHT influence on the intensity of DA synthesis and DA content in the striatum is based on an embryological relationship between chromaffine cells of the sympatho-adrenal system (including CB) [Smitten, 1972] and melanocytes of the SN, which are derived from the neural crest. In this way, the above-mentioned hypothesis could make the method of IHT attractive enough for the achievement of a positive therapeutic effect during non-pharmacological correction of PD.

CONCLUSION

This chapter presents human and animal experiment evidence showing a beneficial therapeutic effect of IHT which may lead to the non-pharmacological correction of PD. Substantial disturbances of locomotive control, particularly respiratory muscles, in PD patients are associated with abnormalities in dopamine synthesis in the central nervous system. Adaptation to IHT is accompanied by an essential activation of tyrosine hydroxylase and by the synthesis of dopamine precursor DOPA. We showed for the first time that IHT enables to normalise lung ventilation in PD patients which is close related to neuromuscular control of respiratory skeletal muscles. Besides, the marked shifts in HVR vs. HCVR in elderly healthy people and PD patients can testify to the direct IHT effect on arterial oxygen chemoreceptors – carotid bodies and/or chemoreflex pathways. Physiological effects are accompanied by positive clinical dynamics in PD patients. Thus, IHT can be successfully used for training/treatment of elderly people and PD patients.

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