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SHORT TERM OXYGEN THERAPY EFFECTS IN HYPOXEMIC PATIENTS MEASURED BY DRAWING ANALYSIS

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Abstract

Background: Chronic hypoxemia has deleterious effects on psychomotor function that can affect daily life. There are no clear results regarding short term therapy with low concentrations of O_2 in hypoxemic patients. We seek to demonstrate, by measuring the characteristics of drawing, these effects on psychomotor function of hypoxemic patients treated with O_2 .

Methods: Eight patients (7/1 M/F, age 69.5(9.9) yrs, mean (SD) with hypoxemia (P_a O_2 62.2(6.9)mmHg) performed two drawings of pictures. Tests were performed before and after 30 min breathing with O_2.

Results: Stroke velocity increased after O_2 for the house drawing (i.e. velocity 27.6(5.5) mm/s basal, 30.9(7.1) mm/s with O_2 ,mean(SD), $p<0.025$, Wilcoxon test). The drawing time 'down' or fraction time the pen is touching the paper during the drawing phase decreased (i.e. time down 20.7(6.6) s basal , 17.4(6.3) s with O_2 , $p<0.017$, Wilcoxon test).

Conclusions: This study shows that in patients with chronic hypoxemia, a short period of oxygen therapy produces changes in psychomotor function that can be measured by means of drawing analysis.

Keywords

Respiratory hypoxemia, psychomotor function, drawing analysis.

BACKGROUND

Chronic hypoxemia has deleterious effects in neuro-psychological and muscle function, with consequences in absent mindedness, perception, and realization of motor tasks [1]. These cognitive and motor function consequences can affect both daily life and relationships with surroundings. The underlying causes of cognitive and motor effects due to chronic hypoxia are a state of chronic systemic inflammation accompanied by oxidative stress directly affecting the neurons, with an increase in neurotransmitters. We posit that oxygen therapy would increase the concentration of oxygen at the brain, which should improve the physiological state of the areas related to cognition.

There are no clear results regarding the effect of low concentrations of O_2 on cognitive state in hypoxemic patients. Some studies did not report any effects and others described positive ones [1,2,3,4,5,6]. Pretto et al showed that acute oxygen therapy did not improve cognitive and driving performance in chronic hypoxemic pulmonary obstructive disease patients (COPD) [6]. Conversely, regular use of supplemental oxygen therapy decreased the risk for cognitive impairment in patients with COPD [1]. It is probable that the difference among these results is due to the fact that tests are not completely sensitive to O_2 changes, or are dependent on disease severity [7]. There is however unanimity regarding their effect on the improvement of life expectancy or on variables such as the 6 minute walking test, red cell number or arterial lung pressures [8,9,10] . On the other hand, hypoxemic COPD seems to have a cognitive impairment profile different from that of normal and demented subject**s**, with verbal memory and praxic/executive function being the most affected, as shown by Antonelli et al [7,1]. The aim of this study was to propose a method that can be done in the patient's home, does not require specialized health technical support and reflects the fine motor brain control [11].

MATERIAL AND METHODS

Eight patients (7/1 M/F), who had hypoxemia more than five years participated in the drawing task study. All had completed primary education and were in a stable condition. All studies were performed by the same physician. The study was conducted in the Respiratory Function Laboratory at Germans Trias i Pujol University Hospital (HUGTIP), and approved by the Human Research and Ethics Committee of the hospital. All participants gave written informed consent as required by the Institutional Review Board, following the World Medical Association's Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Participants were without any diagnosis of writer's cramp. The exclusion criteria were: current smoking habit, high caffeine consumption, hand tremor, neurologic, rheumatic or endocrine diseases and history of drug or alcohol abuse, as well as central nervous system or psychiatric disorders. Neurology and psychiatric disorders were discharged by respective departments.

At baseline, lung function was measured by spirometry (Hyp'Air Compact, Medisoft). Measurements were obtained in accordance with the established guidelines and results compared to normative data [12,13]. Arterial radial gasometry was measured by means of a Gen Premier 3000 analyzer (MedWrench. Bedford Massachusetts. USA) at basal and after 30 min. with O_2 at 3 l/min by nasal plugs.

Drawing analysis was made using a digitizing tablet with an ink pen (Wacom Co, $Intuos_4$,US). All drawing tasks were performed on A4 size liner paper attached to the tablet surface. The drawing tasks reflected perceptual-motor complex functions and cognitive aspects that appear when copying a new figure never seen before. A total of 2 exercises were

carried out, repeating them three times before and after 30 minutes with nasal O_2 at 3 l/min, continuing with O_2 administration during the second part of the test. A complete test session took two and a half hours, and was performed between 09:00 - 11:30 AM. Researchers asked patients to perform drawing tasks: two pictures (a house, a clock). A thirty second interval was given between the single trials.

The digitizing tablet acquires 200 samples per second, including the spatial coordinates (x,y), the pressure, altitude and azimuth [14]. The digitizer provides accurate measurement when the pen is touching the tablet and when it is lifted 6 mm above the digitizer [15].

The analyzed parameters were: pressure, mean velocity, acceleration, time down, time up, entropy, first and second derivatives of pressure and entropy. Mean speed was calculated as positional coordinate x and y derivatives, with respect to time according to:

$$Mean(velocity) = mean\left(\sqrt{\left(\frac{dx}{dt}\right)^2 + \left(\frac{dy}{dt}\right)^2}\right)$$

Where x and y are the spatial coordinates of object drawing.

Time down is the time when the pen rests touches on the tablet and time up is the time with the pen off the tablet.

Mean pressure was measured towards the writing surface in continuous non-scaled units from 0-2047 [16].

Entropy H(X) was calculated considering that the random variable X consists of several events, which occur with probability p(x) and can be calculated according to the equation [17]:

$$H(X) = -\sum_{x \in X} p(x) log_2 (p(x))$$

In the present study, entropy was calculated for the first and second derivative of pressure. Entropy measures the information contained in a signal. Thus, entropy of pressure is the information content of the pressure profile executed by the drawer and is measured in bit units, after applying $\log_2$.

Statistical analysis:

Descriptive statistics (mean, standard deviation, 95% of confidence interval, intra-subject coefficient of variation), were used to describe the variables. Non parametric tests for paired data were applied (Wilcoxon matched pair test and Friedman ANOVA). For comparisons, a probability less than 0.05 was considered as significant.

RESULTS

Table 1 shows anthropometric, demographic and spirometric characteristics of hypoxemic patients. Mean age was 69.5(9.9) yrs, mean height was 164.1 (8.11) cm, and mean body max index (BMI) 24.9(4.1) kg/m^2. All patients were ex-smokers with a mean of 30 packs/year, except for the woman who never smoked. All patients had a moderate-severe airway obstruction except for the female who was affected by an idiopathic pulmonary fibrosis, and patient three who had undergone a thoracoplasty. Patient eight had also undergone a left pneumonectomy for non small cell lung cancer. Spirometric parameters showed an obstructive airway disease characteristic of COPD except for patient 3. COPD, idiopatic pulmonary fibrosis and thoracoplasty are chronic respiratory diseases. These patients developed periodic controls in the consult of pulmonary department and it is usually to practice spirometric and gasometric tests as a clinical control measure.

Arterial blood gases are expressed in Table 2. After 30 minutes breathing O_2 with nasal plugs ,there was a mean increment of arterial P_aO_2 of 31.9 mmHg and 1.2 mmHg of $P_a CO_2$.

Tables 3 and 4 show the results of Kinematic parameters measured by two picture tests: the house and the clock. Velocity and acceleration for the house picture increased with O_2 . There were no significant changes of these parameters for the clock picture test. Hand pressures for house and clock did not significantly change with O_2. Entropy for first and second derivatives of pressure increased with O_2 therapy in both picture tests. Time down decreased with O_2 with respect to basal values for the house test, while time down and time up decreased for the clock test.

An ANOVA non-parametric Friedman test was applied to determine if there was a learning factor between the basal tree test of basal registered. Neither drawing showed significant differences for these variables, except for time down of clock picture ($p<0.03$).

DISCUSSION

In this work we studied the short term effects of oxygen-therapy in the psychomotor state of a group of patients with chronic hypoxemia by means of drawing analysis. Kinematic parameters such as velocity, acceleration and drawing time improved after 30 minutes of nasal O_2.

Krop HD et al was the first to observe the effect of 24 hr treatment O_2 in COPD with hypoxemia. After 1 month the patients improved motor and perceptive functions, as well as memory functions. Cognitive flexibility, motor operations and an increase of grip force are some of the changes that take place after treatment [4,18]. In other studies that used brief periods of O_2 (20 minutes/6h), the authors did not find significant cognitive changes or motor driving performance improvement [19,6]. These studies indicate than the effect of O_2 has been demonstrated in the half and long term, but not in the short term. In our study, time down, or pen time spent on the tablet and time up, or time with the pen off the tablet, decreased during the drawing of clock and house pictures. Pictures are prolonged visu-spacial tasks that need more time to develop. The shorter drawing time is an indirect measurement of decreased necessity for planning drawing tasks, and consequently more efficient drawing.

We did not observe changes in drawing pressure after inhalation of O_2 with respect to basal in complex tasks, as is the case of picture drawings. We believe that a decrease in hand drawing time and kinematic variables without changes in hand pressure could be an indirect manifestation of an improving efficiency of hand drawing as a consequence of O_2 inhalation. While the hand pressure is the same, the entropy which measures the complexity of the drawn picture increases, indicating that subjects develop tasks with more precision using the same energy.

We sought to explain the causes of improvement in psychomotor function after a short oxygen therapy in hypoxemic patients. Chronic hypoxemia involves motor skills, perceptual learning and problem solving, and along with memory are some of the altered functions [20]. These functions can improve, as occurs in patients with severe OSAS (Obstructive Sleep Apnea Syndrome) subjected to night hypoxia that present cognitive alterations in learning, memory and diurnal somnolence [21]. In these patients, treatment with oral appliance or CPAP improves these cognitive functions, suggesting a partial reversibility [22,23] . On the other hand, the alteration of writing can be reversible, as in the case of micrography, which appears after a stroke when it affects the basal ganglia, and disappears in several weeks. Parkinson's, a disease characterized by bradykinesia, tremor, rigid muscle and postural imbalance, when treated with Levodopa, produces an improvement of the coordination, velocity and writing acceleration [24]. In consequence, other causes that affect writing and drawing, such as cellular neural hypoxia, could be partially reversible when we treat the hypoxemia. These changes can be apparent when examining kinematic variables of writing as in our case, where velocity and acceleration drawing decreased with O_2 [25]. For example, substances such as caffeine improve the fluency of handwriting movements and also increase maximum velocity and maximum positive and negative accelerations [26,3,27]. Other substances like nicotine can enhance psychomotor performance of motor tasks to a significant degree [28].

In consequence, it seems logical to conclude that a short O_2 administration in hypoxemic patients could improve the cortical motor function areas. These areas are constituted by: primary motor area (area-4) that controls writing pressure, the supplementary motor area (SMA, area-5) responsible for writing planned movement, and the pre-motor area (area-6) which acts as a visual guide, regulating time and distance. In

addition, the prefrontal area, fundamental in decision taking, is activated when the subject pays attention during the realization of visual and emotional cognitive complex tasks [29]. This area is broadly connected with temporal and inferior parietal cortex, specialized respectively in visual information (shape, size and color) and space localization. Left parietal area recalls graphic images of letters [29]. This area is affected in chronic hypoxia and is related to a reduction of acetyl choline transferase in the same way as the hippocampus and cerebellum, which are the most sensitive areas to hypoxia [30,31]. Basal gangly is fundamental in the brain control of fine movement. The damage of direct and indirect striate-palide ways leads to disordered writing and hippocampus that are related with striate and affected by chronic hypoxia [31,32]. The cerebellum, also affected during the chronic hypoxia, provides the position at the beginning of initiation of hand movements, essential to calculate the time that is needed to execute hand movement. An additional function that can be affected by hypoxia is the hand movement coordination, when comparing the current movement with the movement desired when writing. All these areas try to achieve a more efficient movement in complex tasks, as is the case of drawing pictures.

Several issues related to methodology of the present paper must be addressed. First, the reduced group of patients has not permitted us to draw general conclusions. These patients had different respiratory diseases, including COPD in most cases**.** Second, a high inter-subject variability in kinematic parameters could produce statistical biased results. Moreover, our study compared theses parameters in the same subject in two situations with and without external O_2. To decrease the possible effect of intra-subject variability, tests were repeated three times before and during O_2 administration, and the mean of three attempts to compare results was used. We do not discard the likely existence of the learning factor. Repeating picture drawings could improve the drawing precision and in consequence produce changes in the kinematic variables, but we only found basal significant changes in the time down of the clock picture. For that, we believe that the majority of kinematic

variable changes were not caused by the learning effect. Furthermore, we did not carry out a third test for cleaned O_2 for two reasons: not knowing how long O_2 cognitive effects last, and also taking into account that the procedure time could be excessively prolonged for patients. Four, in some patients O_2 inhalation increased P_aCO_2 levels. Although this could be the cause of some drawing results, principally in drawing pressures, these changes occurred in all patients regardless of P_aCO_2. We did not include a healthy control group and compare it with hypoxemic patients, with limitations in performing two arterial punctures in healthy subjects being the reason. We believe it to be unethical to provide therapy for those not requiring it. It seems probable that an excess of oxygen in healthy people will increase oxidation, aging, etc.

Conclusion

In patients with chronic hypoxemia, a short period of oxygen therapy produces changes in psychomotor status that can be measured by means of drawing analysis. Changes in kinematic parameters demonstrated an improvement in drawing efficiency for complex tasks. Drawing analysis could constitute a method to measure the psychomotor status in chronic respiratory patients treated with different therapies.

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COMPETING INTEREST

The authors declare that they have no competing interest.

FINANCIAL COMPETING INTEREST

There are not financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript. This work was not supported by any grant or other financial disclosures.

Authors' Contributions

JAF: Participated in the design of study, statistical analysis and writing manuscript.

MF: Participated in the design of study, statistical analysis and writing manuscript.

EM: Participated in the design of study, statistical analysis and writing manuscript.

JRA: Participated in the drawing analysis program and help in design and writing manuscript.

FA: Participated in the design of study and help in writing manuscript.

RG: Participated in the design of study and arterial gasometry measure.

JR: Participated in the design of study, statistical analysis and help in writing manuscript.

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Anthropometry and spirometry parameters of 8 patients with chronic hypoxemia

patient		Sex	Age (ys)	High (cm)	Weight (kg)	F EV_1 l. (%)	FVC l.(%)	F EV_1 /FVC (%)
1	**Idiopatic Pulmonary Fibrosis**	F	82	157	71	0.56 (32)	0.85(33)	68.5
2	**COPD**	M	66	168	85	0.83(26)	1.56(36)	53.4
3	**Thoracoplasty**	M	78	155	69	0.81(35)	1.25(38)	64.7
4	**COPD**	M	77	170	72	0.93(30)	1.79(41)	51.7
5	**COPD**	M	61	153	62	1.36(54)	2.19(64)	62.0
6	**COPD**	M	52	170	50	1.56(43)	3.78(79)	41.0
7	**COPD**	M	68	165	85	0.82(26)	1.48(36)	55.3
8	**COPD, Pulmonectomy**	M	72	175	70	0.90(25)	1.61(34)	55.6

TABLE 1

COPD: Chronic obstructive pulmonary disease

FEV_1: Forced Expiratory Volume in a second

FVC: Forced Vital Capacity

Arterial blood gases of 8 patients with chronic hypoxemia before and after 30 minutes with 3 l/min of nasal O_2.

		Basal				Post O_2 (30min, 3l/min)			
		$P_a O_2$ (mmHg)	$P_a CO_2$ (mmHg)	pH	Sat O_2 (%)	$P_a O_2$ (mmHg)	$P_a CO_2$ (mmHg)	pH	Sat O_2 (%)
1	**Idiopathic Pulmonary Fibrosis**	53	46	7.46	89	110	47	7.45	99
2	**COPD**	69	43	7.39	93	89	46	7.38	97
3	**Thoracoplasty**	56	49	7.42	89	86	51	7.43	97
4	**COPD**	65	43	7.42	93	107	41	7.45	98
5	**COPD**	54	37	7.43	89	67	39	7.43	94
6	**COPD**	67	39	7.47	94	100	43	7.45	99
7	**COPD**	64	43	7.42	92	74	43	7.44	95
8	**COPD, Pulmonectomy**	70	52	7.41	94	110	52	7.41	99
	Mean(SD)	62.2 (6.9)	44.0 (4.9)	7.45 (0.02)	91.6 (2.3)	94.1 (18.1)	45.2 (4.6)	7.43 (0.02)	97.2 (1.9)

TABLE 2

COPD: Chronic Obstructive Pulmonary Disease

Cinematic handwriting parameters from eight patients with hypoxemia measured measured from house picture

HOUSE	Pre			Post			
	Mean(SD)	95% IC	CV(%)	Mean(SD)	95% IC	CV(%)	*p
Pressure	1009.54(224.96)	821.47-1197.62	7.9	947.90(227.21)	757.94-1137.85	7.8	0.092
Velocity mm/s	27.65(5.55)	22.95-32.3	15.5	30.95(7.15)	24.95-36.90	11.3	**0.025**
Aceleration mm/s^2	17.00(4.65)	13.10-20.90	10.6	14.15(4.15)	10.65-17.60	16.6	0.050
Time up(s)	15.68(6.66)	10.16-21.20	31.2	13.18(6.11)	8.07-18.28	15.4	0.069
Time down(s)	20.66(6.60)	15.09-26.23	13.4	17.40(6.31)	12.13-22.68	9.1	**0.017**
Entropy dpm	4.59(0.31)	4.33-4.85	7.6	4.97(0.20)	4.81-5.14	4.6	**0.012**
" ddpm	3.91(0.36)	3.61-4.22	9.2	4.30(0.36)	4.00-4.60	4.9	**0.017**

*Wilcoxon Pairs Test . *p: p-value for the paired test.

TABLE 3

Pre, Post: Cinematic handwriting parameters from eight patients with hypoxemia measured from house picture before and after 30 min (3l/min) with O_2 therapy. Pressure: Mean pressure in non-scaled units from 0 to 2048. Velocity and acceleration of hand writing in mm/s and mm/s^2. Time up: Mean writing time off the paper in seconds. Time down: Mean writing time on the paper in seconds. Entropy dpm: Mean entropy of first derivative pressure in bits. Entropy ddpm: Mean second derivative pressure in bits.

CV(%): Mean intra-subject variation coefficient of variation for three tests in percentages. 95% (IC): 95% Confidence Interval for the mean. SD: Standard deviation.

Cinematic handwriting parameters from eight patients with hypoxemia measured from clock picture

ClOCK	Pre			Post			
	Mean(SD)	95% IC	CV(%)	Mean(SD)	95% IC	CV(%)	*p
Pressure	951.26(189.80)	792.56-1109.95	9.6	931.81(207.14)	758.64-1104.98	9.0	0.326
Velocity mm/s	38.15(6.55)	28.65-47.65	11.2	42.7(8.60)	33.85-51.60	11.8	0.886
Aceleration mm/s	18.75(4.65)	13.25-24.20	15.0	18.65(4.15)	11.45-25.90	14.9	0.050
Time up	14.90 (8.68)	7.65-22.15	19.4	10.88(5.20)	6.53-15.22	13.8	**0.017**
Time down	12.95(7.73)	6.49-19.41	13.4	10.76(7.48)	4.50-17.02	7.5	**0.012**
Entropy dpm	5.29(0.35)	5.01-5.58	4.3	5.55(0.0.35)	5.26-5.84	3.1	**0.012**
" ddpm	4.63(0.32)	4.37-4.90	6.4	4.91(0.34)	4.62-5.19	4.3	**0.012**

*Wilcoxon Pairs Test . *p: p values for the paired test.

Table 4

Pre, Post: Cinematic handwriting parameters from eight patients with hypoxemia measured from clock picture before and after 30 min (3l/min) with O_2 therapy. Pressure: Mean pressure in non-scaled units from 0 to 2048. Velocity and acceleration of hand writing in mm/s and mm/s^2. Time up: Mean writing time off the paper in seconds. Time down: Mean writing time on the paper in seconds. Entropy dpm: Mean entropy of first derivative pressure in bits. Entropy ddpm: Mean second derivative pressure in bits.

CV(%): Mean intra-subject variation coefficient of variation for three tests in percentages. 95% (IC): 95% Confidence Interval for the mean. SD: Standard deviation.

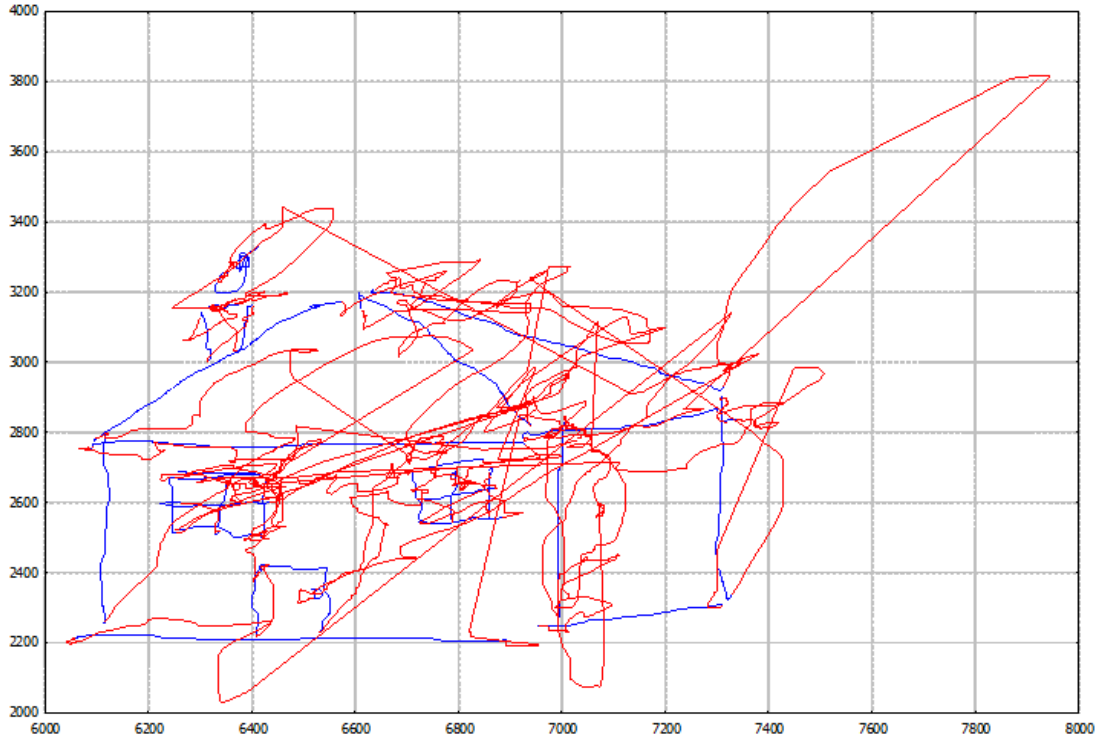

Figure 1

Task of drawing a house picture. Heavy lines are the pen in contact with the paper. Faint lines are with the pen in the air.

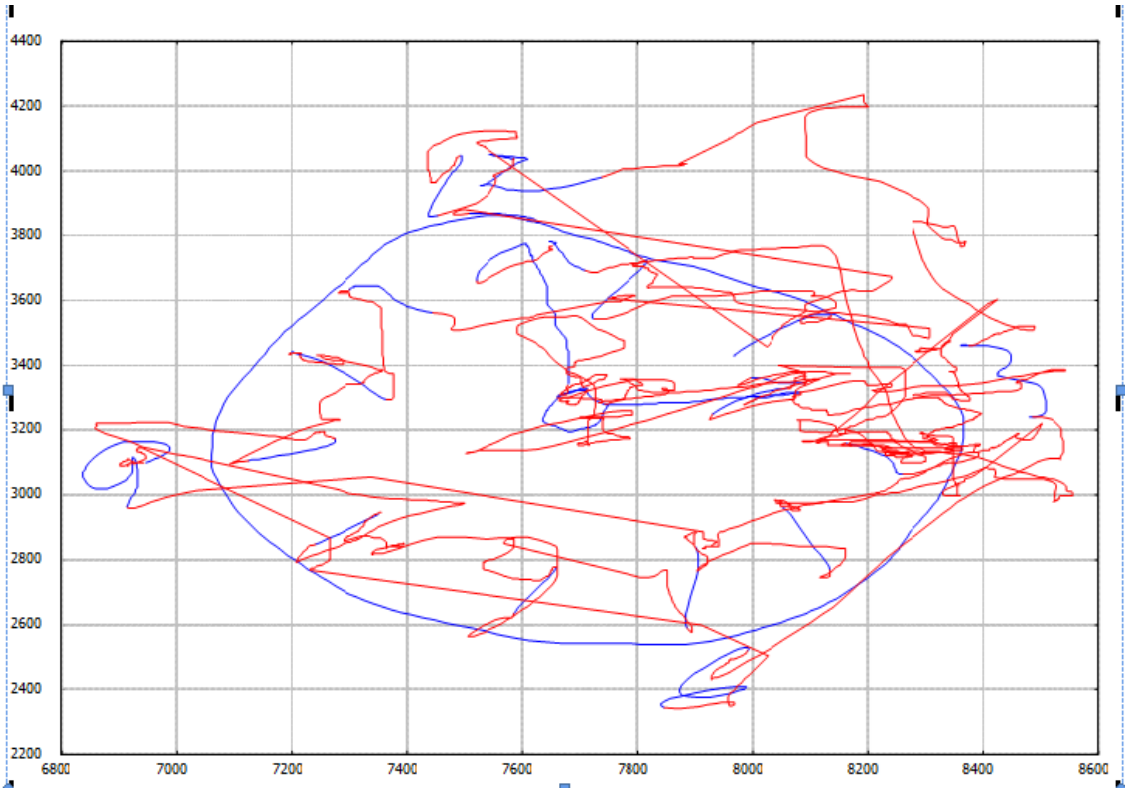

Figure 2

Task of drawing a clock picture. Heavy lines are the pen in contact with the paper. Faint lines are with the pen in the air.