UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

SYNOPSYS OF DOCTORAL THESIS

CHARACTERISTICS TO HYPOBARIC HYPOXIA ADAPTATION, ASSESSED BY ELECTROPHYSIOLOGICAL PARAMETERS

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The Content of Paper

KEY WORDS

Impedance Cardiography (IC), Cardiac Output (CO), Stroke Volume (SV), Heart Rate (HR), Oxygen Saturation (SaO_2), Respiratory Rate (RR), Blood Pressure (BP), Hypobaric Hypoxia.

The thesis contains a number of 161 pages and is structured as follows: Part I - State of Art, accounting to 30% of the original work and Part II - Personal Contributions of 70%. The number of tables showing the results is 113 and the number of charts is 101. It contains 154 bibliographic titles, including 50 in the last 5 years.

INTRODUCTION

Exposure to hypobaric hypoxia is a principal method for aeronautical personnel expertise, because of its synthetic characteristics (by evaluating resistance, training and adaptive synergies of the test subject).

We planned this study because in our country have not been done such research, considering it a useful aeronautical personnel selection and expertise tool on the one hand and useful for hypoxia training in hypobaric chamber for other categories (climbers, athletes, etc.) on the other hand.

This proposed test is quite new, a non-invasive method, tested in the clinical setting by many authors; the originality we aim through this research in hypobaric conditions is the screening of all aeronautical personnel at various stages of hypobaric conditions, data interpretation being made on a broad range of parameters. We conducted a former study, which showed a good correlation between cardiac output measured by bio-impedance and by echocardiography (Vlad 2009).

The importance of knowing complex functional parameters and follow their evolution during exposure to hypobaric hypoxia, is a goal for all medical institutions that participate in aero medical expertise and beyond, having also other implications in sports medicine, rehabilitation etc..

Assessment of human body adaptation to hypoxia by the impedance cardiography method, in conjunction with other physiological parameters in simulated flight conditions, will contribute to a better understanding of the cardiovascular and respiratory responses to hypobaric hypoxia effort, and, in the particular, to understand the negative influence of smoking in these circumstances.

In literature, this technique was used especially in clinical setting, but this time, we aim to give it a different connotation, for healthy subjects, in order to monitor their performance in extreme environmental conditions, hypobaric hypoxia in our case. The method is noninvasive and has a considerable importance in these environments, due to the difficulties of using invasive methods in humans, in the hostile environment.

Bio-impedance as a method for determining stroke volume, was used in astronauts, in early U.S. space program. Being a non-invasive method (one of the main benefits) is more easily accepted in the research laboratories of aviation, both researchers and subjects. It was also used to measure cardiovascular responses to postural stress in high acceleration and microgravity conditions (Cybulski 2011).

The study was conducted over a period of 3 years in the National Institute on Aeronautical and Space Medicine "Gl.dr.av. Victor Anastasiu "- Bucharest (Hypobaric Hypoxia Laboratory) and in the Laboratories of Physiology Department of the Craiova University of Medicine and Pharmacy.

STATE OF ART

Chapter I is a review of the physical properties of the Earth's atmosphere. Hypobaric hypoxia physiology can not be understood without some basics of ground atmospheric composition, its pressure variation and fundamental gas laws.

CHAPTER II features human body particularities under hypobaric conditions. So, there are some of the main functions of the respiratory system, the importance of ventilation, perfusion, and diffusion processes and ventilation-perfusion correlation is shown.

Some details about altitude respiratory function are following, the last chapter being dedicated to the role of various segments of the cardiovascular system in hemodynamic.

Chapter III concerns the parametric evaluation of hypobaric hypoxia adaptation by impedance cardiography.

Also, there are presented the characteristics of impedance cardiography method, last part presenting the technique’s methodological limitations: types of electrodes used, impedance processing equations, testing performed on humans in experimental conditions, specificity and reproducibility.

PERSONAL CONTRIBUTIONS

Chapters IV and V briefly describe the **OBJECTIVES, LOTS, MATERIALS AND METHODS**, used in order to obtain the results.

Objectives:

- Recording the Z_0 impedance wave and its processing in conjunction with electrocardiogram, in order to determine stroke volume;
- Recording together electrocardiogram, oxygen saturation and heart rate with impedance echocardiography;
- Correlation established between smoking and non-smoking status and hypobaric hypoxia adaptation;
- Correlation of results obtained by tracking other cardiovascular and respiratory parameters (blood pressure and respiratory rate);
- Correlations established between anthropometric parameters and balance of physiological parameters, monitored during the test.

Lots:

We selected an initial group of 100 subjects, aged between 23 and 53 years, (Group I), in a clinical and paraclinical healthy status. Young people have been shown to be the most compliant to carry out this study, 44% of the subjects being less than 35. Age distribution histogram based on smoker / non-smoker, does not seem to indicate significant differences.

In order to measure changes in respiratory rate and blood pressure, I have selected a second group (Group II), with 50 subjects, aged between 20 and 51 years. Age distribution histogram based on smoker / non-smoker, does not seem to indicate any significant differences in this group either.

Materials and methods:

All tests were performed in two available rooms in the Hypobaric Hypoxia Laboratory from the National Institute on Aeronautical and Space Medicine. It was the first use in our country, within a hypobaric chamber, of impedance cardiography during hypobaric-hypoxia probes.

For both groups, the parameters registered were amplified using specific modules of the BIOPAC MP150 system.

During the tests, polyphysiographic data records were taken, in the 6 main steps of the standard profile for the hypobaric- hypoxia resistance determination for aeronautical personnel: "GROUND" (before Tests), "5500 m", "BEFORE EFFORT", "DURING EFFORT", "AFTER EFFORT" and "DESCENT".

The data collected was included in the corresponding tables and was statistically processed, using specialized software.

Chapters VI and **VII** were reserved for **RESULTS** and **DISCUSSION**.

After processing the resulting data to test subjects belonging to Group I, age descriptive statistics indicate an average of 37.48 years age with a considerable standard deviation of 8.30. The histogram explained this deviation and showed that age does not follow a normal distribution, with two peaks in the segment 30-35 years and 45-50 years.

The only demographic parameter, apart from age, which I found interesting to monitor, was the difference between smokers and non-smokers.

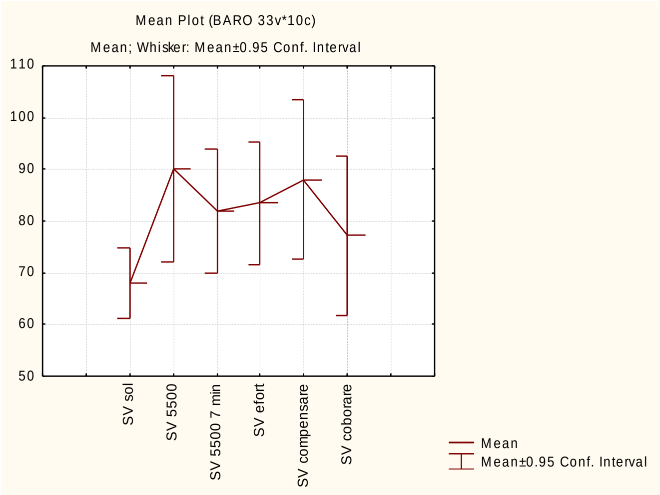
Age distribution histogram based on smoker / nonsmoker showed no clear differences by ANOVA test. One conclusion that emerges is the existence of a large number of smokers at young ages, which shows that both educational measures in the general population and specific in aviation organizations are not as effective as they should be.

Statistically, smoker / non-smoker, is the only categorical variable in our study and this type of analysis was done for all continuous variables.

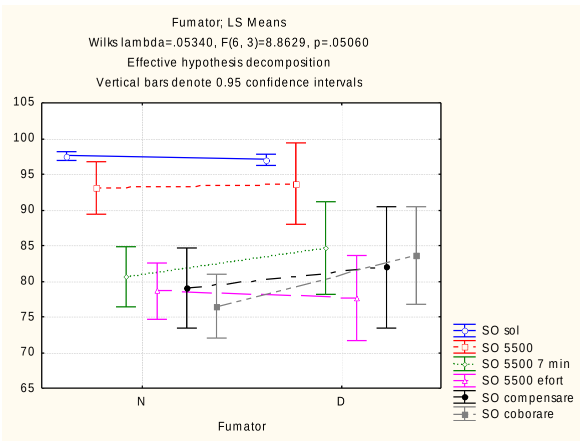
Regarding cardiac output measured “on the ground”, at rest, in the studied group was observed that smoking had no influence on it.

Regarding heart rate, there is an influence of smoking on heart rate at rest, but this is minimal, statistically insignificant.

Regarding systolic volume, the difference is minimal. Given the direct relationship between cardiac output, heart rate and stroke volume (CO = HRxSV), low statistical significance of the difference in heart rate must be countered by a very small difference as statistically significant for systolic volume to justify the values obtained for cardiac output . This comment applies to all triplets CO, HR, SV, in all the stages of exposure to hypobaric hypoxia.



Regarding the oxygen saturation between smokers and nonsmokers, we have observed that the average saturation for smokers is 97.75%, compared to non-smokers, 97.45. These results are consistent with the literature data (Roth, 2011, Wittig, 2008), which shows that the oxygen saturation measured by pulse oximetry may be higher in smokers, due to the adaptive polyglobulia. Throughout the test, it was observed that oxygen saturation values do not show significant differences between smokers and nonsmokers. In "DESCENT", there is a significant difference in oxygen saturation, although small, reverts to the ground the pattern, indicating that, in our study, at rest or at the end of adaptive challenges, smokers have a better oxygen saturation, if only marginal. Although this seems to be justificative for smoking, it should be noted that this advantage disappeared during adaptation, which proved deficient. Increased blood O2 saturation may be an adaptive mechanism to chronic cigarette smoking, by an increase in red cell mass, leading to false results (Smith, 1978, Tirlapur, 1983, Powers, 1989, Buckley, 1994).

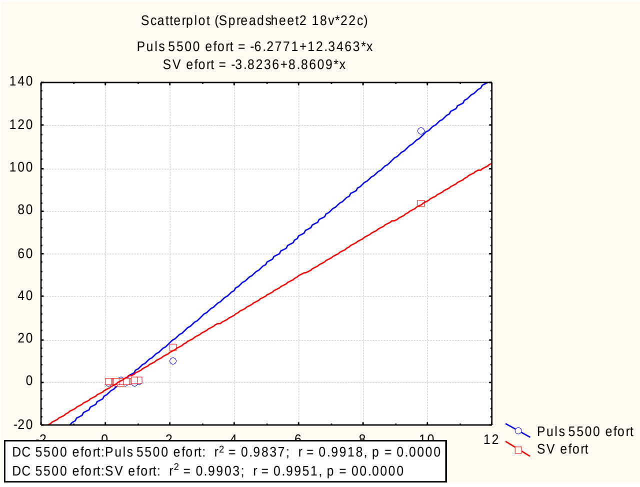


Brosnan (2000) does not identify changes in SaO_2 at maximal effort, in hypoxia, although the difference is significant in long-term effort. Similarly, athletes do not register changes in heart rate during effort. Submaximal effort leads to an increase in heart rate, as well as an increase in muscle lactic acid (Van Hall 2009).

The amount of lactate monitoring is controversial, due to changes in acid-base balance induced by hypoxia (Mc Lellan 1990).

Bender (1989) identifies the expected drop in oxygen saturation in acute exposure to hypoxia at submaximal effort, but it is corrected since the second day. On day 22, after adjustment, reach 80% against 73% in the second day, paradoxically, both maximal oxygen consumption and ventilation remaining constant.

At effort, cardiac output in smokers vs nonsmokers was approximately in the same value range. During the maximum effort compensatory intervention, the ratio smoker vs nonsmoker is physiologically unimportant. Similarly, the value of heart rate during exercise does not show significant differences between smokers and nonsmokers, only a greater dispersion in smokers. Systolic volume appears to be significantly different, however, with lower values in smokers.



From the "F" and" p" values during different moments, we conclude that, overall, smoking has a specific role only on the GROUND and immediately after exposure to altitude. In other words, adaptation to hypoxia may be related to smoking, but the effort is too demanding and smoking becomes a negligible factor.

Hoon (1977), studying a group of 50 subjects, observed a decrease in stroke volume at altitude, with a slow recovery in 4-5 days, followed by a further relapse on the tenth day. The initial decline is explained as an adaptive mechanism, the biochemical basis is shown by Howald (1990), as a decrease of mitochondrial oxidative activity.

Decreased number of mitochondria is, after Zhang (2008), a process of mitochondrial autophagy. However, there no studies on human myocardium, to identify this mechanism (Holloway 2011).

Allemann (2000) proves, by two different methods, an increase in pulmonary artery pressure. Ricart (2005) observes Sidenafil effect on pulmonary pressure.

However, adapted individuals have minor increases in pulmonary artery pressure, which, moreover, subsides promptly at oxygen administration (Dubowitz 2009).

Another mechanism is shown by Kelly (2008), that identifies decreased protein synthesis at the cellular level as an additional factor of reducing the useful cardiac mass in hypoxia.

Another finding in the experiment at Everest base camp (Holloway 2011), is a reduction of ventricular mass by 11%, following a prolonged hypobaric hypoxia. Similar results were reported by Howald (2003) by anthropometric and biochemical study conducted on Himalayan Sherpas.

Hoppeler (1990) identifies morphological changes of skeletal muscle, but, paradoxically, the capillary network remained unchanged, implying that the adaptation mechanism is vascular rather than cellular.

The peak after effort appears probably on increased duration of diastole, reducing heart rate (Garpestad 2004 Koskolou 1997 Boussuges 2000). Oxygen saturation starts to drop sharply after the increase in altitude and remains low. Peak during exercise is probably explained by changing hemoglobin dissociation curve, in terms of effort hypoxia.

Hansen (2003) shows a reflex sympathetic activation in hypobaric hypoxia, but only at skeletal muscle level. Indirect evidence of cardiac sympathetic activation comes from Buchheit (2004), which shows decreased heart rate variability in exposure to hypobaric hypoxia.

Lundby (2001) identifies a decrease in maximal heart rate during prolong exercise, corresponding with the increase in altitude, in unchanged sympathetic activation conditions, that can suggest a local mechanism.

For Group II, the results were of low significance for BP (systolic and diastolic), the only specific change being increase of respiratory rate, more in smokers than in nonsmokers, which is corresponding with literature data.

Blood pressure in smokers vs non-smokers shows no statistical significance or is poorly correlated. Systolic blood pressure (SBP) has increased steadily over the test, with a peak immediately after effort, probably during the effort too, but technical constraints did not allow the collection of data under these conditions. Diastolic blood pressure (DBP) follows a similar line, more attenuated. The data collected, did not permit us to assess relation between DBP increasing and fluid retention or dehydration, controversial terms in hypobarism (Hoyt 1991).

Results on BP values in hypobarism are controversial on human’s studies because of methodological deficiencies and direct influence of hypobarism to technical system (Huston, 1947, Stenberg 1966). However, direct measurement by catheterization, in chicken (Owen 1995), identifies BP increase, not directly related to the change of respiratory rate (RR). Our data support these observations, with the notable exception of the EFFORT phase.

Teppema (2010) shows that despite the absence of ventilation’s decline, there was a small decrease in tidal volume, but compensated by an increase in RR, enhanced by exercise.

As a conclusion of previous reviews, maximum cardiovascular taxing was not during "pure" hypobaric hypoxia, but during effort, especially at the submaximal one.

As a practical application, dosing effort to hypobaric hypoxia has interesting effects in sport medicine (Clark 2007). Gore (2005) promoted the concept of "live high, train low" that brings optimal balance between cardiovascular and muscular adaptation drawbacks and benefits of adaptation to hypoxia, by increasing resistance to hypoxia and stimulation of erythropoiesis.

We believe that the results are interesting because, through them, we validated one more time the method to 5500 meters effort, as an additional exploration in barochamber, from classic profiles of over 7,000 meters (Valdez 1990) and opens new perspectives for the study of the benefit adaptation to hypoxic stress in other areas of aviation physiology, such as high-gravity environments overload.

Chapter VIII is reserved to the **CONCLUSIONS**:

1. Our study was initiated due to the need to complete the range of tests used in the assessment of aeronautical personnel adaptation to hypobaric hypoxia, by using impedance cardiography method. The test provides relevant data on the variations of the cardiac output, of its triggering factors, and it is being used for the first time nationally in healthy subjects tested in hypobaric hypoxia conditions.

2. Among the parameters that define cardiac output, heart rate marked, from baseline (GROUND), an increase to values of 121 c / min, during EFFORT - the differences were not statistically significant, demonstrating adequate aeronautical

personnel adaptation to hypoxia.

3. Systolic volume values ranged from 88 ml at ground to 83 ml during effort, registering a statistically insignificant decline of the parameter in testing stages, explained by reduced ventricular filling phase due to increased heart rate.

4. Due to changes in its determinants, cardiac output shows a quasi-linear increase during exposure to hypoxia, compared to the values recorded on the ground (7 l/min), with a maximum at effort (10 l/ min).

Return to baseline correlates with changes in blood oxygen saturation, slower immediately after exercise and accelerated during the descent.

5. Blood oxygen saturation, parameter that expresses true hypobarism influence has dropped significantly from the reference values (ground test) - 89% to a minimum of 81% at an altitude of 5500 m. In effort test we found an increase due to displacement of the oxyhemoglobin dissociation curve to the right, due to local tissue changes, accentuated under hypobaric hypoxia.

6. Monitoring of respiratory rate, during the test phases, shows its growth from resting values of 14 c/min to 21 c/min, immediately after exercise in hypoxia (altitude 5500 m), change explainable by paying the "oxygen debt" accrued by cardiorespiratory adaptation to increased oxygen needs of the body in the stage of effort.

7. This study followed the influence of factors such as age, experience and flight hours and smoking on adaptation to hypoxia in the aeronautical personnel. Although the changes of the mentioned factors were not statistically significant, it requires a special mention for smoking, which affects exercise capacity in hypoxia and less resistance to such conditions.

Complex testing of a group of subjects, with features that meet the requirements of appropriate statistical processing, revealed the importance of impedance cardiography as an investigative method, with a significant contribution to objective assessment of aeronautical personnel adaptation to hypobaric hypoxia conditions.

An additional merit refers to the national originality of the study of monitoring flying personnel with impedance cardiography noninvasive test, properly applied in the laboratory under simulated hypobaric hypoxia.

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