CHARACTERISATION AND PRACTICAL IMPORTANCE OF EXERCISE- INDUCED CARDIOVASCULAR RESPONSE

IN a 6 - TO 18-YEAR-OLD POPULATION

Ph.D. Thesis

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Introduction

„Many seminal longitudinal cohort studies have clearly shown that the antecedents to adult disease have their origins in childhood…societies have called for more rigorous, evidence-based guideline development to aid primary care providers and subspecialists in improving recognition, diagnosis, evaluation, and treatment of pediatric hypertension”.

Although hypertension and consecutive cardiovascular diseases (CVD) are leading morbidity and mortality causes worldwide, and provenly often starts in childhood; juvenile hypertension still remains underdiagnosed. Hypertension arising from child and adolescent age can already lead to organ damage, CVD or even early mortality already during the active years. Accordingly, the early recognition of the main risk groups for early disability and mortality, due to their hypertension, would enable timely, targeted intervention either by personal lifestyle guidance or medical treatment. This way the number of consequential CVD in young adulthood could be decreased.

These recognitions justify the necessity of new approach to hypertension diagnostics and development of new ways of screening.

In our work we integrate novel results of hypertension research and knowledge about applicability, diagnostic and predictive value of juvenile exercise stress test.

Everyone has seen a student lagging behind others at a PE class, but nobody could say whether it is laziness, or there are other reasons behind their weak cardiopulmonary fitness. For this reason, first, we determined the characteristic change of heart rate and blood pressure of the population after the distance-running test, which can be considered as a maximal aerobic stress for children. Next, in a pilot project, we explored the possibility of recognizing the risk population and those hypertonic students based on deviation of blood pressure, whose condition remained undetected by regular screenings.

As a next step, we have developed an easy-to-use, low-budget screening method, that was able to identify pupils belonging to risk groups and special hypertension cases. During the pilot project, our cut-off values were determined based on national and international guidelines considering the parameters of the total population.

Because of the effect of obesity on blood pressure, age and sex specific cut-off points have been modified in international child hypertension guidelines by excluding overweight and obese children from the base population. In the light of that, we deemed it necessary to determine standard age and sex specific values for normal weight population.

With precise description of a low budget and easily used method and publishing of age and sex specific standard values, this is the first publication of hemodynamic effects of field exercise test on a large healthy population. This provides the means for international comparison of under-stress hemodynamic parameters of both under the 12 years old and the above 12 years old population.

With establishment of age and sex specific exercise induced hemodynamic changes of a healthy school-aged population, we took a step towards classification of abnormal and healthy values in every case, even without correctly answering the original question: is it caused by laziness or by other reasons? But it is also true, that more children could be classified with CVD risk and consequently allowed to prevent their disease.

Determining a standard interval opens up possibilities for identification of risk groups, thereby for early, targeted and efficient prevention and intervention. This might decrease the frequency of one of the most significant endemic groups, of cardiovascular diseases.

Objectives

In spite of the fact that hypertension and consequential cardiovascular diseases are a major cause of worldwide mortality and morbidity and increasing evidence prove that it initiates in childhood, it is not properly diagnosed in this population.

In order to establish the clinical usefulness of hemodynamical response to exercise testing in children and adolescents with HT, a larger body of data is needed. In order to achieve this, we aimed to:

1. Establish the characteristics of exercise induced changes of blood pressure and heart rate in the general population of students between 6-18 years, during an easily reproducible, widely used exercise test

2. Study the applicability of the exercise induced haemodynamic changes for screening test for early detection of special hypertension types, with establish a school and exercise-based, CVD screening method.

3. Define reference values of haemodynamic changes of healthy, normal-weight, in the 6 - to 18-year-old population, during a field exercise test. Present a dataset for anthropometric and hemodynamic parameters measured both before and after the exercise, and after five and ten minute recovery times.

Participant characteristics

This investigation was conducted as a prospective, multicenter study in 3 Hungarian cities (Hódmezővásárhely, Mártély and Mindszent), in South-East Hungary between 2007 and 2018. In order to exclude the possibility of error in the selection of the examined subpopulation, we aimed to accomplish a comprehensive survey of the students of Hódmezővásárhely, which is the most populated of the three cities. Population: 43,700 (2018) mainly Caucasian type, (self-declaration basis, CSO census: in the region, 1.9% Roma population, other races do not occur in larger numbers). Inward and outward migration was negligible in the period under review. Till 2011, 26,963 measurement sequences, 10,692students were tested and used as reference for the whole population pilot project.

At 2018 we had 102,642 data acquisition points from 14,267 individuals (7,239 boys, and 7,028 girls), out of which 65,345 acquisition points of 10,894 individuals

were selected to establish the reference values for the population with normal weight

The involvement in the anthropological measurements in the school is compulsory for everyone. Participation in physical education is also mandatory (except for those, who are exempt from exercise) for all students. The additional BP parameter measurements before and after the running-test were optional, but no one opted out, all participants gave consent.

Measurement Protocol/Data Collection

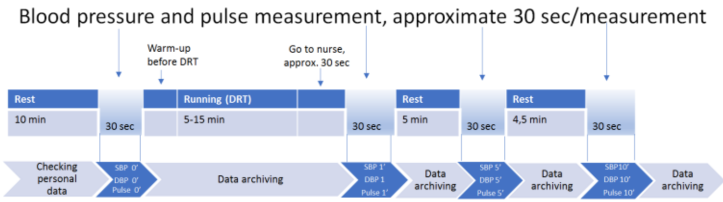

Figure 1. Measurement/Fit-test Protocol. The duration of the whole experiment was approximately 40-45 minutes. Four pulse (P), systolic (SBP) and diastolic blood pressure (DBP) measurement were collected per subject during a single Fit-test.

The anthropological measurements carried out before the running test. Blood pressure and pulse values were measured with a validated, automatic blood pressure monitor, in accordance with the daily practice of school screening and the MHT protocol. The whole class was surveyed at the same time, with an average of 20-30 students. A nurse group (of 10 to15 nurses) performed blood pressure and heart rate measurements on the tables alongside the track. The student's blood pressure and heart rate were measured on a chair with a back rest, with a comfortably placed arm, at heart level (SBP 0’, DBP 0’, Pulse 0’).

During the test, under the supervision of physical educators, everyone had to run 1,000 meters (1-4 classes age between 6-10) or 2,000 meters (5-13 classes age between 10-18) as fast as possible on the same 400 meters (0.24 miles) long, flat, oval outdoor runway. The PE teacher measured the running time with a manual stopwatch and recorded the result of the run. After completing the distance, the student immediately went to one of the nurses who measured her/his blood pressure (SBP 1’, DBP 1’, Pulse 1’) and informed her/him of the time of his next measurement, which was taking place at 5 and 10-minutes after exercise (SBP 5’, DBP 5’, Pulse 5’ and SBP 10’, DBP 10’, Pulse 10’), and the data immediately recorded All BP measurement carried out once in each point in time.

De-identification

To make our experience internationally comparable and to analyze its generalizability, we have created a high-quality, normal population dataset, in line with the latest international guidelines.

In the process of creating the dataset, all identifiable personal information has been removed. Each individual thus has only an ID which links the measurements at different corresponding dates in the database.

Generation of normal population hemodynamic dataset

Since obesity and being overweight influence cardiac parameters, we included only the normal-weight subpopulation to generate a representative exercise-induced cardiac parameter dataset. The WHO criteria (-2 to +1 SD z-scores) were used to identify the normal weight population. The running speed was calculated using the running time and distance values of the dataset.

From this normal subpopulation dataset, we also excluded the outlier measurements of the hemodynamic (before/after exercise pulse, SBP and DBP) and running speed based on the 1.5 IQR method.

A high-quality normal population dataset was distributed to make it internationally comparable to analyze the generalizability of our experience

The datasets are distributed in the normal standard file formats (text, xlsx) and can be read and processed by a variety of commonly used statistical packages, including SPSS, Matlab, Python, and R.

Results

Haemodinamic effect of DRT in the general school age population

Characteristics of heart rate and blood pressure induced immediately after DRT and in the restitutional period were investigated.

10 692 students were measured from 2007 to2011 and their 26 963 measurement sequences were included for the characterisation of haemodinamic parameters in resting state and after DRT. The hemodynamic parameters of the whole population at rest and their changes due to DRT were determined.

Exercise heart rate (HR)

Due to the effect of DRT, the degree of change in the resultant pulse and blood pressure measurements compared to those of the starting point.

There is a significant difference observed between HR changes in individual children due to exercise, but overall, they show a normal distribution. 90% of students had a heart rate increase between 11/min and 79/min. The average was 44.9/min (SD 21.8/min) n: 26,920. The background of excessively high or low pulse increase, or the decrease of it, can be a measurement error or, less likely, too low or too excessive exertion, occasionally for health reasons.

Recommended target HR

Recommended target HR helps in evaluating whether the physical exertion was appropriate for a given student or a group. The attained HR in the course of exercise is linked to individual categories according to age and level of physical condition**.**

Recovery heart rate

After 10 minutes of recovery the recommended HR is 10% more than pre-run HR. 16,5% of the examined population of pupils belongs to this group. 4,5% of them produced lower HR than that. For them the trial was less burdening than their daily routine. HR of 83,5% however stayed higher than required.

Pupils' HR, raised by DRT, remained high after 10 minutes rest, in numerous cases, in 83,5% (p< 0,001; average: 22,4/min; SD: 13,5; n:26938). We can interpret that for the majority (83,5%) of pupils this trial meant **a bigger load than their actual fitness levels were able to safely tolerate.**

Exercise Blood Pressure

After DRT most of the children produced a higher BP than before, similarly to the change of pulse rate. (Fig.4.A). Average SBP rise: 20,8 mmHg (SD: 16), p<0,001, n=26599. DBP rise at the same measurements: 1,86 mmHg (SD:12,14) mmHg. SBP rise at 65% of the pupils was between 10-40 mmHg immediately after DRT. We also experienced exaggerated BP rise, which could be an early sign of HT, which predicts future hypertension

Recovery Blood Pressure

Average difference of SBP values measured before and 10 minutes after running: -5,8 mmHg (SD: 12,2 mmHg) median -5,0 mmHg; p <0,001 (FIG. 6/B). Meeting with expectations, there was a decrease of BP comparing to the values measured before the load in 61% of cases, in 17% the values are essentially the same as the initials (difference less than 2 mmHg), and only at 22% of the cases showed higher BP values than at the beginning.

Comparison of resting and exercise blood pressure values by age and gender

In the study population, the mean blood pressure of boys and girls is approximately the same between the ages of 6 and 12 years, with a difference of 1-2 mmHg in favor of boys. However, from the age of 13, the trend lines are separated. 13-year-old boys have SBP higher than girls with 3mmHg. The difference grows steeply and steadily until it reaches 12 mmHg by the age of 17y. Exercise SBP also moves together in both sexes up to 12 years of age, with a difference of 1-2 mmHg in favor of boys. At 13 years of age, boys have 4 mmHg of high blood pressure, and the difference continues to increase until the age of 16, when they reach 14 mmHg. Boy-girl differences and the slope of trend lines are similar for resting and loaded SBP values.

Comparison „Fit-test" DRT and Kiel EX.PRESS graded cycle test

Both of the studies agree in the following statements:

The mean blood pressure of boys and girls is approximately the same at12 years, both before and after exercise. Seemed a year-by-year increase in difference of resting and peak blood pressure of males after 13 years of age, compared to SBP of females of the same age, in favor of males. Boy-girl differences and the slope of trend lines are similar for resting and loaded SBP values. Exercise mean SBP values of males of 14 years of age is approximately 150 mmHg. Boys reach peak exercise SBP of approximately 160 mmHg at the age of 16 years. Trend lines of exercise values follow idle values for both sexes over age

Define reliable, simple screening method: Fit-test, as a screening pilot project

We measured the hemodynamic effect of DRT on students, and every pupil’s individual data was classified to normal values of population by gender and by age. In our work, we applied BP elevation - induced by physical exercise and physiological load of our school survey - to screen the risk of HT and found that exercise-related screening was also suitable for examination of MHT, preHT, and HT students, proven by the specific cases.

E-health

Development and deployment of E-health solutions reduced administration time, improved data capture accuracy, solved challenges with the immediate, non-human data transfer and statistical analysis of data, facilitating their understanding and use of access rights of stakeholders and eligible persons.

Fit-test.hu, website

Students and their parents, numerically, with info graphics and textual explanations, were able to view their fitness and health results on a web interface. Where appropriate, they also received lifestyle advice or suggestions for medical consultation. GP, school physician and specialists could see the data through the same IT system with percentile values and graphs to assist with accurate diagnosis. Regular and system-wide, multidisciplinary screening, with equal access, may call attention to screening for blood pressure, abnormal leanness and overweight, deterioration of general fitness, or respiratory, hematopoietic, hormonal, cardiac or renal diseases.

Specificity, sensitivity

Specificity of screening test: 0.998, Sensitivity: 0.83, Positive predictive value for hypertension: 0.58. In addition, among false positive cases there are students with prehypertension, requiring additional care and monitoring.

Compliance:

At first year of special screening only 57% of pupils presented at check up from the identified and four years later it was 77%. The method of medical checkup also was very different. It can be stated that due to the lack of consensus therapies and of connection between the individual care sites, screening is often not followed up adequately, and therapeutic habits are not uniform, meaning that the guidelines are not always followed.

Obese students are five times more affected in elevated BP in this population according to our study.

According to an anonymous questionnaire survey 90 -96% of students (in both primary and secondary schools) consider daily physical activity and early detection of illness to be important. This is a good basis for this generation to have regular exercise later in life and to undergo regular screening tests.

Data Records

In the complete datasets at 2018, we provide repeated measurements on the same individuals of various anthropometric and hemodynamic parameters (102,642 records) of a large (14,267 participants) school-aged (6-18 years of age) cohort. It is prospective over 8 years (3.44 (SD 2.92), and 7.19 (SD 5.21) datapoints of participants). The anthropometric dataset can be used to analyze age and sex-dependent BMI changes leading to either obesity or normal body weight to identify risk-groups and proper time of intervention.

Anthropometric dataset of 6-18-year-old children

The *fit_database_anthropometric_all.xlsx* is deposited in the anthropometric_all folder. Each data record contains the individual ID (that links different time series measurement dates of the same individual), measurement date, age (in years), age bin (age category in years), gender, height (cm), weight (kg) values, the calculated BMI, WHO z-score and WHO z-score categories of 102,642 data acquisition points from 14,267 individuals (7,239 boys, and 7,028 girls).

The calculated gender- and age-specific height, body weight and BMI percentiles (1, 3, 5, 10, 25, 50, 75, 90, 95, 97, 99) and the corresponding number of individuals in this dataset can be found at the XLSX table: ***percentiles_anthropometric_all.xlsx***.

BMI and WHO z-score calculation

The BMI was calculated by the formula of $BMI = \frac{weight}{height^2}$ The WHO z-scores were calculated by the methodology described in[51], using the WHO age and sex normalized LMS reference tables[52]). The z-score weight categories were determined according to the rules set by WHO (z-score < -3 - severely thin, -3 <= z-score < -2 - thin, -2 <= z-score < 1 - normal, 1 <= z-score < 2 - overweight, 2 <= z-score - obese). We also calculated the standard deviation (in range of -3 to +3) of experimental BMI values in our dataset for all age and sex categories. Using the WHO criteria (-2 to +1 SD) we identified the normal-weight subpopulation.

Cardiovascular parameters before and after the DRT in the normal-weight children's population

In order to determine the cardiovascular parameters in a student cohort with normal weight 10,894 students were selected (65,345 acquisition points)

Fit-test allowed us to monitor the changes in the cardiovascular parameters before and after the DRT in normal-weight (age and gender separated) reference children and young adolescent (6-18 years of age) population. The normal weight cardiac parameter dataset can be used as a standardized reference chart, to develop complex strategies utilizing exercise-induced parameters to screen for cardiovascular abnormalities.

The datasets are distributed in the normal standard file formats (text, xlsx) and can be read and processed by a variety of commonly used statistical packages, including SPSS, Matlab, Python, and R.

- Haemodynamic effect also has individual (fitness and health specifics) and population-level (public health impact) relevance to exercise.

- Confirmed evidence about the pupils: differences exist between recovery HR and recovery BP trends: recovery HR remained at a high level, in contrast, the recovery BP decreased to starting level or below.

- Established a pilot, exercise-related screening test, called “Fit-test”. It provides an opportunity to gain new insight into the relationship between later manifestations of illness and juvenile burden response.

- Fit-test is a low-budget, whole-population screening test, which easily fits into an existing school and school health system.
- We have found that is also suitable for screening for MHT, preHT, and sustained HT students, and for monitoring the effects of treatment.

- We established a **database, the first large dataset of haemodynamic changes of normal-weight pupils during a field exercise test**.

- We defined the population-specific dynamics and experienced individual dissimilarities.
- It provided an opportunity to evaluate the physical and cardiovascular fitness together.
- Established a possibility for subsequent monitoring of the health status of the affected generation, and risk group.

This dataset is useful for physical education teachers, coaches, physicians and exercise physiologists to evaluate actual cardiovascular fitness and haemodynamic responses to exercise in children or adolescents and follow its change.

List of papers related to the subject of this thesis

I. K. Havasi; M. Katona. Testnevelés órai terhelésre adott cardiovascularis válasz populációs szintű elemzése és gyakorlati jelentősége. Gyermekgyógyászat 66, 24–28 (2015)

II. K. Havasi; Cardiovascularis prevenció az iskolában. in Az elsődleges gyermekorvoslás gyakorlata (ed. Mihály Kálmán, Á. K.) 217–220 (Kft, KM-PharmaMédia Kiadó, 2015).

III. K. Havasi; M. Katona; Cs. Bereczki. A sokarcú hypertonia. Új szemléletű iskolai szűrővizsgálat, mint cardiovascularis prevenciós modell,

Gyermekgyógyászat 69.,

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IV. K. Havasi; Z. Maróti; A. Jakab; I. Raskó; T. Kalmár and Cs. Bereczki

Reference values for resting and post exercise hemodynamic

parameters in a 6–18 year old population. Sci. Data 7, 26 (2020).

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