RISK FACTORS AND HEART RATE VARIABILITY AS THE PREDICTORS OF CARDIOVASCULAR DEATH: TEN YEAR HEALTH OUTCOMES COMMUNITY–BASED STUDY

Jurgita Andruškienė, Aurelija Podlipskytė, Arvydas Martinkėnas, Giedrius Varoneckas
Behavioral Medicine Institute, Lithuanian University of Health Sciences, Lithuania

Summary
The aim of this study was to compare the prevalence rates of coronary artery disease risk factors between two surveys conducted in 2003 and 2013 in the community-based sample of Palanga citizens and to evaluate the risk factors and heart rate (HR) variability as the predictors of cardiovascular death.

Material and methods. The prevalence of CAD risk factors in a 35–74 year old representative sample of Palanga was assessed in 2003 (N=1602) and 2013 (N=931). CAD risk factors were evaluated according to WHO recommendations. Maximal HR response to standing during orthostatic test was assessed. Cardiovascular death data for the period of 2003–2013 was obtained from Civil Registry Department of Palanga Town Council and Institute of Hygiene. Direct standardization method of CAD risk factors prevalence according to age/gender-adjusted rate was performed. The comparison of proportions between two groups was performed using z-test. Cox proportional hazards regression analysis was performed to assess how CAD risk factors and HR variability parameters increase the risk of cardiovascular death. P-values less than 0.05 were interpreted as statistically significant.

Results. Significant increase in hypercholesterolemia was observed from 74.9 % in 2003 to 78.2 % in 2013. Prevalence of smoking was significantly lower in 2013 (17.2 %) compared to 2003 (25.8 %). Arterial hypertension (HR=2.73), regular smoking (HR=2.18) and older age (HR=1.10) increased the risk of cardiovascular death significantly among males. Older age (HR=1.19) predicted cardiovascular death among females. Decreasing maximal heart rate response to standing ($\Delta$RR$_B$) increased the risk of cardiovascular death in the whole sample (HR=0.95) and among males (HR=0.94).

Conclusions. Cardiovascular death was predicted by arterial hypertension, increasing glucose level in blood, regular smoking, older age, male gender and reducing heart rate response to orthostatic test.

Keywords: risk factors, heart rate variability, predictor, cardiovascular death, health outcomes, community.

INTRODUCTION
Cardiovascular diseases (CVD) are ascribed as chronic non-communicable diseases, as well as diabetes, cancer and chronic pulmonary diseases [1]. The Framingham study was a landmark study that, already in the 1960s, gave strong evidence as to the likely causal role of several lifestyle-linked factors in the development of CVD. Men in Finland had at that time the highest mortality rates of coronary artery disease (CAD) in the World. In 1972, a pioneering project by a young leadership team and many partners, including World Health Organization, was started to change the situation [2]. The Framingham Study has provided insights into the prevalence, incidence, prognosis, predisposing factors and determinants of CVD. Well-established risk factor concept, fundamental to prevention of CVD, originated from the Framingham study. It generated findings such as the effects of tobacco use, unhealthy diet, physical inactivity, obesity, raised blood cholesterol, arterial hypertension and diabetes on CVD [3]. Diet and nutrition have been extensively investigated as risk factors for CAD and stroke and are also linked to other cardiovascular risk factors like diabetes, arterial hypertension and obesity [4].

In the developing countries, all-cause mortality will increase from 56 % (2005) to 65 % (2030), in developed countries from 87.5 to 88.5 %, respectively [1]. The WHO has signaled a shift from the treatment of illness to promotion of health, with an emphasis on changing modifiable health-risk factors, including smoking, unhealthy diets and physical inactivity [5].
The experience of diminishing the prevalence of risk factors in the population is a powerful demonstration of how the CVD epidemic can be successfully confronted [2]. Over 80 % of CAD and type 2 diabetes and 33 % of cancers could be prevented by changes in lifestyle factors, including diet, weight maintenance and physical activity [6]. The most prevalent risk factor of CAD in the population of city of Palanga in 2003 was hypercholesterolemia (74.9 %), reflecting widely spread unhealthy behavior in the community [7]. The main predictors of cardiovascular mortality are very well established; however the role of autonomic heart rate (HR) control evaluated by HR variability is still discussed.

The aim of this study was to compare the prevalence of coronary artery disease risk factors between two surveys conducted in 2003 and 2013 in the community-based sample and to evaluate the risk factors and heart rate variability parameters as the predictors of cardiovascular death.

MATERIAL AND METHODS

Sample. A random sample of 2500 citizens of Palanga aged 35–74 was drawn from the National Population Register in 2002. The citizens of Palanga were chosen as an object of investigation, because there was close community with minor migration reflecting the population of West part of Lithuania. The optimal size of the sample, ensuring representativeness of the population of Palanga aged 35–74 years, was calculated (1630±33 individuals). From the sample of 2500 citizens, 160 selected persons were not invited to participate in the study, because they were not found at the given addresses, 1602 persons (600 males and 1002 females) participated in the survey in 2003. The response rate for the first survey was calculated in the following: (1602/2340)×100 % = 68.5 %.

In the period from 2003 until 2013, 158 persons of those, who had participated in the first survey in 2003, died (9.9 %), 47 (2.9 %) people had changed their address, 20 (1.2 %) declined to participate, 11 (0.7 %) could not participate as a result of serious health problems, and 435 (27.2 %) people did not respond to the multiple invitations sent to them by post. During the second survey, data from 931 people, 322 males and 609 females, aged 45–84 years, were collected. The first and the second surveys were approved by the Bioethics Committee of Lithuania. Informed consent was obtained from all participants during both surveys.

The mean of age of the first survey participants was 55.0 years (SD=10.5), the second survey – 63.8 years (SD=10.5), respectively. Distribution of the respondents according to gender did not differ significantly. Greater part of the investigated persons were retired in 2013 (49.1 %, 95 % CI 45.9–52.3), compared to 2003 (33.2 %, 95 % CI 30.9–35.5), but smaller part were unemployed in 2013 (1.8 %, 95 % CI 1.1–2.8), compared to 2003 (6.2 %, 95 % CI 5.1–7.4), p<0.001.

Anthropometric (height, weight measurement and body mass index calculation), arterial blood pressure measurements, biochemical blood analyses, active orthostatic tests and questionnaire surveys were performed twice (in 2003 and 2013) in the same sample, using the same methodology.

Height (cm) was measured with a medical height rod, the person was without shoes. The back and the head were posed close to the measuring scale. The result was registered with the precision of 0.5 cm.

Weight (kg) was measured using medical scales, without shoes with the precision of 100 g. Body mass index (BMI) was calculated according to the following formula: BMI=body mass (kg)/height² (m) using the data of height and weight measurement. Overweight was diagnosed when BMI was 25.0–29.9 kg/m², obesity when BMI was 30.0 kg/m² and more.

Arterial blood pressure (mmHg) was measured twice with a quicksilver sphygmomanometer on the right hand while a person was sitting, with the precision of 2 mm referring to the methodological recommendations [8]. The average of two measurements was used for the analysis. The participants were classified as hypertensive if their systolic blood pressure was ≥140 mmHg and/or diastolic arterial blood pressure ≥90 mmHg, or they received antihypertensive drug treatment for the last two weeks.

Biochemical total cholesterol, high density lipoproteins cholesterol, low density lipoproteins cholesterol, triglycerides and glucose tests in blood serum were performed in the laboratory of biochemical research. The participants had been warned in advance to come not having intake of food at least 12 hours. Blood was taken from the elbow vein directly to vacuum blood collection systems, while the person was sitting (amount – 7 ml). Cholesterol concentration in blood serum was measured by ferment (CHOD – PAP) method. Hypercholesterolemia was defined when total serum cholesterol was ≥5.0 mmol/l, increased glucose level was stated when glucose was ≥6.1 mmol/l.

HR variability was assessed using active orthostatic test (standing-up from supine position) and HR power...
spectrum analysis during quite supine. Maximal HR response to standing (difference between average HR during supine and maximal HR during standing), reflecting maximal parasympathetic input into the autonomic HR control, was calculated using previously described methodology [9, 10]. This measurement is based by physiological investigation data of D. Eckberg and co-authors demonstrating withdrawal of vagal control of HR during the first seconds of standing-up from supine position [11, 12]. HR power spectrum from HR record in supine position was calculated and very low frequency, low frequency, and high frequency components, reflecting termo-metabolic, sympathetic and parasympathetic regulation were distinguished using previously described methodology [13, 14].

Questionnaires. The questionnaire of General Data was used to collect the information about the age, family status, education, employment and diagnosed diseases, self-reported by the respondents. Information about smoking was obtained by the Questionnaire of health behavior [15]. A person who smoked at least one cigarette per day was considered as a regular smoker. Smoking rates were assessed during the first and the second surveys.

We investigated the main risk factors for cardiovascular death (smoking, arterial hypertension, hypercholesterolemia, increased glucose level in blood, overweight and obesity), confirmed by epidemiologic study results [16, 17], during both surveys, in 2003 and 2013. Other risk factors, such as physical inactivity, dietary imbalance and alcohol use were not analyzed.

Cardiovascular death data in the sample during the period of 2003-2013 were obtained from Civil Registry Department of Palanga Town Council and Institute of Hygiene. Cardiovascular death cases were confirmed by the codes of I20-I25 (deaths caused by CAD according to 10th International Classification of Diseases), I60-I69 (deaths caused by stroke), I00-I99 (deaths caused by other cardiovascular diseases, except I20-I25 and I60-I69). During the period of 2003–2013 there were 83 death cases (32 (38.6 %) of them were in females), caused by CAD, stroke or other cardiovascular diseases.

Statistical analysis. Age-standardized prevalence changes of CAD risk factors rates in the 2003 and 2013 were calculated and presented with 95 % confidence intervals (CI). Direct standardization method of CAD risk factors prevalence according to age/gender-adjusted rate was performed. For 2003 year, for age strataums 35–44, 45–54, 55–64, 65–74 age/
Employed persons more often had hypercholesterolemia in 2013 (77.6 %, 95 % CI 73.8–81.2), compared to 2003 (72.2 %, 95 % CI 69.5–74.9), p<0.05. Females more often had AH in 2013 (77.6 %, 95 % CI 73.8–81.2), compared to 2003 (72.2 %, 95 % CI 69.5–74.9), p<0.05. 45–54 years old persons less often had AH in 2013 (28.9 %, 95 % CI 23.9–34.1), compared to 2003 (46.3 %, 95 % CI 41.5–51.2), p<0.001, as well as 55–64 years old persons, 53.8 %, 95 % CI 47.8–60.1 vs. 64.3 %, 95 % CI 59.2–69.1, p<0.05, respectively.

**CAD risk factors and the risk of cardiovascular death**

Arterial hypertension (HR=2.73), regular smoking (HR=2.18) and older age (HR=1.10) increased the risk of cardiovascular death significantly among males (Table 2, Model 1). Older age (HR=1.19) predicted cardiovascular death among females.

**Table 2.** Hazard ratio for cardiovascular death in the whole sample (2003), among males and females

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>The whole sample (N=1602)</th>
<th>Males (n=600)</th>
<th>Females (n=1002)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95 % CI)</td>
<td>Hazard ratio (95 % CI)</td>
<td>Hazard ratio (95 % CI)</td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>3.05 (1.82–5.12)</td>
<td>3.05 (1.82–5.12)</td>
<td>3.05 (1.82–5.12)</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.13 (1.09–1.16)</td>
<td>1.10 (1.04–1.14)</td>
<td>1.19 (1.11–1.27)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.88 (1.06–3.33)</td>
<td>2.73 (1.31–5.73)</td>
<td>0.94 (0.37–2.38)</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>1.17 (1.04–1.30)</td>
<td>1.14 (1.00–1.29)</td>
<td>1.19 (0.96–1.49)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.27 (1.20–4.27)</td>
<td>2.18 (1.09–4.38)</td>
<td>1.22 (0.16–9.69)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>1.02 (0.97–1.07)</td>
<td>1.00 (0.93–1.07)</td>
<td>1.04 (0.96–1.12)</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>0.96 (0.79–1.17)</td>
<td>0.90 (0.70–1.17)</td>
<td>0.98 (0.71–1.35)</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>3.34 (1.92–5.81)</td>
<td>3.34 (1.92–5.81)</td>
<td>3.34 (1.92–5.81)</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.12 (1.08–1.16)</td>
<td>1.09 (1.04–1.13)</td>
<td>1.18 (1.09–1.27)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.61 (0.87–2.97)</td>
<td>2.65 (1.18–5.96)</td>
<td>0.95 (0.34–1.95)</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>1.27 (1.10–1.47)</td>
<td>1.28 (1.06–1.53)</td>
<td>1.16 (0.91–1.48)</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.37 (1.20–4.68)</td>
<td>2.15 (1.01–4.58)</td>
<td></td>
</tr>
<tr>
<td>RR, ms</td>
<td>0.99 (0.94–1.05)</td>
<td>0.95 (0.88–1.03)</td>
<td>1.05 (0.96–1.15)</td>
</tr>
<tr>
<td>RR, ms</td>
<td>0.99 (0.99–1.00)</td>
<td>0.99 (0.99–1.00)</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>VLFC, %</td>
<td>1.00 (0.98–1.02)</td>
<td>1.00 (0.98–1.03)</td>
<td>0.99 (0.96–1.04)</td>
</tr>
<tr>
<td>LFC, %</td>
<td>1.00 (0.97–1.03)</td>
<td>0.98 (0.94–1.02)</td>
<td>1.017 (0.97–1.06)</td>
</tr>
<tr>
<td>∆RR, %</td>
<td>0.96 (0.92–0.99)</td>
<td>0.95 (0.90–0.99)</td>
<td>0.93 (0.90–1.05)</td>
</tr>
</tbody>
</table>

**Discussion**

Hypercholesterolemia in our study demonstrated high prevalence, however was not confirmed as the predictor for cardiovascular death. This finding contradicted the study analyzing the data of 900,000 healthy at the baseline adults in Western Europe and North America, which proved positive associations between total cholesterol and CAD mortality in both middle and old age participants [18]. The difference might be explained by the comparatively small sample in our study.

Regular smoking and arterial hypertension were proved as the predictors of cardiovascular death. This finding was in line with the recently published scientific results, emphasizing that prevention of smoking [19] and arterial blood pressure control [20] are extremely important in the prevention of premature death.

Decreasing maximal heart rate response to standing increased the risk of cardiovascular death in our study, it corresponded to the publications demonstrating the association between decreased maximal HR response to standing and cardiovascular pathology [21–23]. This finding did not surprise us,
but it was the first attempt in Lithuania to evaluate HR parameters in the community as the possible predictors of cardiovascular death. Our study gives a scientific evidence as a support to idea of using HR variability monitoring as the initial screening of cardiovascular risk in the general population. This idea is not new, it was already highlighted in the scientific literature [24, 25], when HR variability monitoring was recommended to use in a primary health care practice as a non-invasive, economical and easily implemented.

Contrary to Finbalt Health Monitor study [15], conducted in the representative sample in Lithuania containing 4000 persons (20–64 years old), prevalence of overweight and obesity did not change significantly during the decade in the sample representing population of the city of Palanga. The prevalence of overweight has increased in the sample of Finbalt Health Monitor survey from 52.0 % in 2002 to 61.1 % in 2012. The differences could be explained by age differences of the samples.

Arterial hypertension prevalence rates, demonstrated in our study (55.6 % among females and 48.4 % among males in 2013) were similar to the prevalence rates of AH among females (44.6 %) and males (60.3 %) in the sample, representing five rural regions (Kaišiadorys, Kretinga, Kupiškis, Joniškis and Vareṇa) of Lithuania [26]. Small differences could be influenced by the geographical health inequalities, influencing higher prevalence of health risk factors in the rural regions, as compared to urban ones.

Prevalence of AH during the period of ten years demonstrated no significant changes during a period of ten years, it contradicted the results of the survey, conducted in the population of Czech Republic, which demonstrated downward trend in population’s mean systolic (from 133.6 ± 20.2 to 128.8 ± 18.1 mmHg; p<0.001) and diastolic (from 84.1 ± 11.3 to 71.4 ± 10.0 mmHg; p<0.001) arterial blood pressure over a period of 15–16 years [27].

The findings of our study could be used as a scientific background for planning specific primary prevention interventions and providing recommendations for health policy makers, primary health care team and the community of Palanga, aiming to control risk factors of chronic non-communicable diseases. Our study results confirmed the necessity to control arterial blood pressure, glucose level in the population and promote nonsmoking behavior. Preventive interventions were implemented in many European countries in the community level, but the most inspiring example was intervention study performed in North Karelia, province in Finland in the year 1970. The effective strategy of primary prevention improved significantly the dietary pattern among citizens of Finland. The use of dietary fat reduced from 90.0 % to 5.0 %. It has led to reduction of blood cholesterol level and significantly decreased (80.0 %) annual CVD mortality rates [28].

**CONCLUSIONS**

1. Hypercholesterolemia was the most prevalent CAD risk factor in the randomly selected sample of Palanga citizens, investigated in 2003 and 2013. Prevalence of hypercholesterolemia increased; while the rates of regular smoking decreased significantly during ten year period.

2. Cardiovascular death was predicted by arterial hypertension, increasing glucose level in blood, regular smoking, older age, male gender and reducing heart rate response to orthostatic test.

Received 12 October 2014, accepted 28 November 2014

**ACKNOWLEDGMENTS**

This study was funded by a grant (No. LIG-03/2012) from the Research Council of Lithuania.

**STATEMENT OF CONFLICT OF INTEREST**

The authors state no conflict of interests.

References


Rizikos veiksnių ir širdies ritmo variabilumų kaip mirties nuo širdies ir kraujagyslių ligų prediktoriai: 10 metų sveikatos išeičių tyrimas bendruomenėje

Jurgita Andruškienė, Aurelija Podlipskytė, Arvydas Martinkėnas, Giedrius Varoneckas

Lietuvos sveikatos mokslų universiteto Elgesio medicinos institutas

Santrauka

Tyrimo tikslas – palyginti išeminės širdies ligos (IŠL) rizikos veiksnių paplitimo rodiklius 2003 m. ir 2013 m. ir įvertinti IŠL rizikos veiksnius bei širdies ritmo variabilumo parametrus kaip mirties nuo širdies ir kraujagyslių ligų prediktorius 10 metų laikotarpiu tarp atsitiktinai atrinktų Palangos miesto gyventojų.


Rezultatai. Hipercholesterolemijos paplitimas didėjo nuo 74,9 proc. 2003 m. iki 78,2 proc. 2013 m. Rūkymo paplitimas buvo statistiškai reikšmingai mažesnis 2013 m. (17,2 proc.) lyginant su 2003 m. (25,8 proc.). Arterinė hipertenzija (SR = 2,73), reguliarus rūkymas (SR = 2,18) ir vyresnis amžius (SR = 1,10) didino vyrų mirties nuo širdies ir kraujagyslių ligų riziką. Vyresnis amžius (SR = 1,19) didino moterų mirties riziką. Mažėjantis maksimalus širdies ritmo pokytis stojant didino mirties nuo širdies ir kraujagyslių ligų riziką visoje imtyje (SR = 0,95) ir tarp vyrų (SR = 0,94).

Išvados. Mirties nuo širdies ir kraujagyslių ligų riziką didino arterinė hipertenzija, didėjantis gliukozės kiekis kraujyje, reguliarus rūkymas, vyresnis amžius, vyriška lytis ir sumažėjęs maksimalus širdies ritmo pokytis stojant ortostatiniu mėginiu metu.

Reikšminių žodžių: rizikos veiksnių, širdies ritmo variabilumų, mirtis nuo širdies ir kraujagyslių ligų, išeičių, bendruomenė.

Adresas susirašinėti: Jurgita Andruškienė
Lietuvos sveikatos mokslų universiteto
Elgesio medicinos institutas
Vydūno al. 4, 00135 Palanga
El. p. jurgita.andruskiene@gmail.com

Straipsnis gautas 2014-10-16, priimtas 2014-11-28