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FREQUENCY OF PATHOLOGICAL  
ELECTROCARDIOGRAPHIC  
FINDINGS AND THE ROLE OF  
ELECTROCARDIOGRAPHIC  
SCREENING IN THE FIRST FORM  
PUPIL POPULATION IN LATVIA

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## ABBREVIATIONS USED

AV – atrioventricular

BMI – body mass index

ECG – electrocardiogram

HCMP – hypertrophic cardiomyopathy

HR – heart rate

ICD – implantable cardioverter-defibrillator

J-NL – *Jervell* and *Lange-Nielsen* syndrome

msec – milliseconds

PQ – PQ interval

PQTS – prolonged QT interval syndrome

QRS – QRS complex

QTc – corrected QT interval

RFCA – radiofrequency catheter ablation

SIDS – Sudden Infant Death Syndrome

SV<sub>1</sub>+RV<sub>6</sub> – sum of S wave amplitude in lead V1 and R-wave amplitude in lead

V5 or V6

WPW syndrome – *Wolff–Parkinson–White* syndrome

# 1. INTRODUCTION

Sudden death among children and youth is a tragic event for both the child's family and for society as a whole. Although sudden death in children is not common an appropriate investigative method for screening of sudden cardiac death risk markers is still being searched for. The literature most frequently deals with sudden death among athletes and in different countries there are different screening algorithms and regular inspections adopted, but there is still no unified position in the investigative tactics of this population. Screening tactics of sudden death in the general population is being discussed in literature and in the societies of cardiologists, but there is no common position with regard to the optimal screening method and the usefulness of such screening at all.

ECG is an inexpensive method, which allows a timely diagnosis of such causes of sudden cardiac death as hypertrophic cardiomyopathy, WPW syndrome, Brugada syndrome, long QT syndrome and others. A number of sudden cardiac death reasons can be diagnosed just by ECG, and by using this method they can be diagnosed at an early stage. It is the timely determination of cardiac death risk that is significant, therefore the first ECG screening should be performed in newborns, however, at this age ECG screening often gives little information since heart rate at this age often limits the identification of specific ECG changes such as Brugada syndrome, hypertrophic cardiomyopathy and others. The next age period when general health check-up is performed, is 6–7 years of age, when children start school. There is no centralized ECG examination for children in this age group in Latvia, and this examination is encumbered with some circumstances – health examination is performed by the general practitioners, who are usually not specialized in children's ECGs, consequently there could be a lot of false positive and false

negative findings in these ECGs. In order to facilitate a centralized ECG examination of pre-school children, it would be necessary to develop an algorithm for defining of abnormal results and for further actions in the cases of detecting certain changes.

So far the most widely used norms of children's electrocardiographic findings variations have been based on the study data of *Davingnon et al* (Davignon, Rautaharju, Boisselle et al., 1979) in the seventies, which analysed electrocardiograms of 2 141 children. They developed the normal range from the 2<sup>nd</sup> till 98<sup>th</sup> percentile of 39 measurements in 12 age groups with an average of 120 children in each group. The application of these and subsequent trial data today and under Latvian conditions, however, is limited and may not correspond to the current situation, for instance – children's physiological differences today compared to those more than 40 years ago. So far no studies have been conducted in Latvia on the incidences of abnormal ECG findings in children, since electrocardiograms (ECG) are not performed in a centralised way, thus the early detection of a number of cardiac pathologies – various degrees of atrioventricular blockades, family cardiomyopathies, etc. – is not possible.

In Latvia no substantiated schemes have been developed so far by which early electrocardiographic screening should be carried out for school age children before starting school and there is no concept about the future tactics in the cases of stating signs of possible risks. The current thesis by means of the statistical methods allows the professionals to determine the norms of the normal electrocardiographic findings expressed in percentiles in Latvia's first - form pupils, it allows the professionals to identify high - risk patients among Latvia's schoolchildren, to predict the spread of diseases among the population and to minimize the potential risk for the life of the children early enough. As a result of the thesis the algorithm of action was developed in the cases of relevant abnormal electrocardiographic findings.

## **2. LITERATURE REVIEW**

### **2.1. ECG changes in infants and children**

Adult ECG interpretation is performed in accordance with generally accepted standards, but in the interpretation of the ECGs in children, the wide admissible variations must be taken into account, which are defined as the standard at a certain age. The fastest changes in children's ECGs happen during the first year of life. In 1979, Davignon and colleagues published the data (Davignon, Rautaharju, Boisselle et al., 1979) of the ECG analyses of a large Canadian children population, taking into account the children' age. The study was conducted in 2 141 Caucasian children from newborns to the age of 16. The children that were examined were divided into the following 12 age groups and the resulting ECG measurements were determined with the 2<sup>nd</sup>, 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 95<sup>th</sup> and 98<sup>th</sup> percentile in each group.

Although a relatively small number of children were included in the study for each age group and almost 40 years have passed since that study, the measurements and percentiles of standards obtained by Davignon and colleagues are still widely used. In adults it has been demonstrated that ECG changes are based on race, ethnicity, and body mass index (Rautaharju, Zhou, Calhoun et al., 1994) – black people have higher QRS voltage than Caucasians, while it is lower for Latinos. Similar correlations have been found in children (Rao, Thapar, Harp et al., 1984; Rao, 1985).

Still controversial are the criteria of left ventricle hypertrophy in ECGs for children. In the multi-center study, which was conducted in the USA by performing ECG and echocardiographic examinations in children with confirmed HIV infection, in children born to HIV-infected mothers and in healthy children's group, it was concluded that the previously adopted signs of

left ventricular hypertrophy ECG are very non-specific. (Rivenes, Colan, Easley et al., 2003) This study found that the QRS voltage standards are higher than those adopted by Davignon and his colleagues. As a result of the study, new standards for QRS voltage in the III and chest leads were developed. In later years *Rijnbeek* and colleagues in Rotterdam conducted a study with a population of 832 children, ranging from newborns to 15 years of age, during the ECG records lead V1 was replaced by V3R and lead V5 with V7. In determining the index of *Sokolow-Lion*, the formula  $R V_{3R} + R V_7$  was used instead of the  $R V_1 + R V_6$  in order to obtain greater specificity of the test, though it was still only 25.3 %. However, in view of the proposed technical details of ECG recording, this method cannot be widely used in general practice.

In the recommendations developed by the American Heart Association in 2009 for a standardized interpretation of the ECG (American College of Cardiology, American Heart Association and the Heart Rhythm Society [ACC/AHA/HRS], 2009) it was acknowledged that the diagnostic ECG criteria of left ventricular hypertrophy in children are still unclear and the research in this field is insufficient, it includes a small number of children and in most cases the child's weight, race, or nationality were not taken into account. The suggested ECG criteria of left ventricular hypertrophy are reflected in Table 2.1.

Table 2.1.

**The American Heart Association's recommendations for the determination of left ventricular hypertrophy**

	Voltage(mV)				
	Age 0-7d	Age 7d-1y	Age 1-3y	Age 3-5y	Age > 5y
$R V_6$	>12	>23	>23	>25	>27
$S V_1$	>23	>18	>21	>22	>26
$S V_1 + R V_6$	>28	>35	>38	>42	>47

\* (ACC/AHA/HRS, 2009)

Children's heart rate (HR) varies with age. In neonates, it ranges from 109 to 150 times per minute. The average speed of the HR after the first week of life slightly increases. When a child grows the heart rate decreases until adolescence when it reaches 58 to 105 times per minute. The data of Davignon and colleagues (Davignon, Rautaharju, Boisselle et al., 1979) demonstrate an inverse relationship between the body surface area and the heart rate. Akiba *et al* (Akiba, Nakasato, Sato et al., 1995) found in their study that left ventricular volume and stroke volume increase with age correlates with the body surface area. HR decrease with the increase of left ventricular volume and stroke volume provides a stable left ventricular ejection dependency on the body surface area. Taking into account the data of Davignon and colleagues, as well as the subsequent wider research data and guideline recommendations, a book was published in 2006 that summarised children's ECG measurement standard percentiles (Lue, 2006).

PQ interval in newborns is shorter than in adults, and it ranges from 94 msec to 127 msec. The lower limit of PQ interval for children is 90 msec, which is lower than for adults – 120 msec. This can make it difficult to diagnose ventricular premature irritability syndrome.

QRS complex amplitude depends on the right and left ventricular mass, cardiac position in the chest, weight and structure. In infants 1 month of age the left ventricle becomes larger than the right one, and in infants 6 months of age it reaches the same relationship between the right and left ventricles as in adult patients (Emery and Mithal, 1961). In spite of the above mentioned, a 6-month-old infant has a different ECG from that of adults (Onat and Ahunbay, 1998). Possibly it is because the babies at this age have generally a vertical orientation of the heart. Therefore in leads V3 and V4 QRS voltage is higher and on the left chest leads it is lower. In view of the newborn heart anatomical peculiarities when the right ventricle mass is greater, QRS axis is shifted to the right and the angle  $\alpha$  is between  $+87^\circ - +181^\circ$ , high R teeth in right chest

leads and deep S teeth on the left leads are observed. Compared to adults, newborns have also a narrower QRS which increases with age.

QT interval which is measured in the II lead from the start of the Q wave till the end of the T wave, depends on the heart rate – the slower the heart rate, the longer the QT interval. Therefore for the standardisation of QT the Bazett's Formula is most widely used (dividing the QT interval in seconds by the square root of the RR interval in seconds) obtaining the QTc measurements that show what QT would be if the heart rate would be 60 times per minute. QTc is on average 440 msec, but it may be extended during the first days of life and return back to normal at the end of the first week (Rautaharju, Zhou, Calhoun et al., 1994). QTc 440–460 msec is considered to be the upper limit, but the QTc > 460 msec should be regarded as a significant extension (Nemec, Hejilik, Shen and Ackeman, 2003). The reasons of QTc prolongation are discussed below.

## **2.2. Prolonged QT interval syndrome (PQTS)**

PQTS is a congenital heart disease which is characterized by QT prolongation in a basic ECG and an increased risk of life-threatening arrhythmias. The estimated prevalence of the disease is 1 per 2 500 live births.

The two main manifestations of the disease are syncope episodes, which can result in cardiac arrest and sudden cardiac death, as well as ECG changes – QT prolongation and T wave changes. Genetic basis of the disease is a mutation in the genes that determine the ion channel functioning of the heart. (Nemec, Hejilik, Shen and Ackeman, 2003). Mutations in these genes (KCNQ1, KCNH2, KCNE1, KCNE2, CACNA1c, CAV3, SCN5A and SCN4B) cause the disease, prolonging the duration of action potential. A prolonged QT interval, which is a transient finding associated with the somatic diseases and use of

certain medications, should be distinguished. Since in this case the reason is adjustable and by eliminating it, the QT interval is normalized, in such cases the prognosis is more favourable.

Congenital PQTS has two clinical variants: one is associated with congenital hearing loss (*Jervell and Lange-Nielsen syndrome*) and the other is not related to hearing impairment (*Romano-Ward syndrome*). PQTS can be divided even by the mutant gene. The most common are LQT1 and LQT2 (mutations in potassium channels) and LQT3 (mutation in sodium channels).

In the seventies of the last century PQTS was considered a rare disease with a prevalence estimated 1:5000 (Nemec, Hejilik, Shen and Ackeman, 2003) to 1:20000 (Moss and Robinson, 2002). However, expanding the scope of research and the research methods, it was proved that PQTS is frequently undiagnosed rather than rare disease. The first extensive study which lasted 30 years from 1976–2007 and included 44 596 infants who were 3–4 weeks old in Italian maternity wards (Stramba-Badiale, Crotti et al., 2007). 1094 infants were discovered with QTc > 440 msec, in 858 of them QTc ranged from 440 to 450 msec. 177 infants had a QTc 451–460 msec, 28 infants had it 461–470 msec and 31 infants > 470msec. It was discovered that this population had 30 infants (1.4 %) with a prolonged QTc between 450 and 469 msec and 28 with QTc > 470 msec. For 90% of these infants the analysis of 7 major PQTS gene mutation was conducted, and if the gene mutation was found, this analysis was carried out in their relatives. The mutations in the genes that determine QT prolongation were discovered in 46 % of babies. Since QTc that is > 440msec is also considered prolonged, it can be said that the prevalence of prolonged QT interval is at least 1/2500.

The triggering factors of arrhythmia are dependent on the mutant gene: for most patients with LQT1 ventricular rhythm disorders often begin under physical or psychological stress conditions. For LQT2 patients the trigger factor most likely is emotional stress (sudden noise, especially if the patient is

at rest), while for LQT3 patients ventricular rhythm disturbances more often are observed at rest ( Schwartz, Priori, Spazzolini, Moss et al., 2001). Greater life-threatening arrhythmia risk is for women in post-natal period, especially for LQT2 patients patientēm (Rashba, Zareba, Moss et al., 1998). T wave variation (*alternance*) in amplitude and its direction is also one of the most important ECG signs in the PQTS case. T wave variability in these patients is associated with physical or emotional stress, but may be also observed at rest and points to electrical instability of myocardium.

The study conducted in 1975 indicated that PQTS patients on average have a lower heart rate when compared to subjects with normal QT interval (Merri, Benhorin, Alberti, Locati and Moss, 1989). PQTS in literature is also viewed as the reason of Sudden Infant Death Syndrome (common abbreviation in the literature SIDS – Sudden Infant Death Syndrome). SIDS is a sudden death of an infant under the age of 1 year and the cause remains unclear even after further investigation (autopsy and medical history of the investigation) (Krous, Beckwith, Byard, Rognum et al., 2004). During the period from 1976 to 1994 the long QT relationship with SIDS was studied in Italian maternity wards (Schwartz, Stramba-Badiale, Segantini et al., 1998). The study included 33 034 infants. The QT interval was identified in the first week of life and for 1 year they were observed with respect to SIDS. Among the studied infants 34 cases of death were found, 24 of them due to SIDS. The infants who died due to SIDS, had a longer QTc interval than the survivors (average standard deviation of  $435 \pm 45$  msec vs  $400 \pm 20$  msec,  $P < 0.01$ ), and infants who had died of other causes ( $393 \pm 24$  msec).

### 2.3. Brugada syndrome

Brugada syndrome is characterized by right bundle branch block, ST segment elevation in ECG and sudden death. It was first described in 1992 (Moss and Robinson, 1992).

There are three types of ECG findings in Brugada syndrome:

1. Type 1 ECG findings: convex ST segment elevation  $\geq 2\text{mm}$  followed by a negative T wave with a low isoelectric separation  $> 1$  in the right chest lead (from  $V_1$  to  $V_3$ ).
2. Type 2 ECG findings: ST segment elevation, followed by a positive or biphasic T wave with a saddle-shaped configuration.
3. Type 3 ECG findings: saddle-shaped or curved ST segment elevation,  $\leq 1\text{mm}$  in the right chest leads.

Although Brugada syndrome can be represented by all the three ECG types for a definite diagnosis of Brugada syndrome the only type 1 ECG may be used. This ECG finding should be linked to:

- 1) documented ventricular fibrillation,
- 2) polymorphic ventricular tachycardia,
- 3) death till 45 years of age in family history,
- 4) type 1 ECG findings for family members,
- 5) the possibility to cause ventricular arrhythmias during intracardiac electrophysiological investigation in a programmed stimulation,
- 6) syncope,
- 7) agonal breathing during the night,
- 8) gene mutation in combination with the syndrome.

If the patient has only a characteristic ECG finding of Brugada syndrome but not the rest of the clinical signs of the syndrome, it should be

viewed as Brugada syndrome ECG findings, but not as Brugada syndrome (Wilde, Antzelevitch, Borggrefe et al., 2002).

Brugada syndrome is a channelopathy that causes the dysfunction of ion channels involved in creation of the action potential of the heart. This electrical dysfunction leads to increased risk of arrhythmia; this disorder is primary and not related to structural heart damage. Brugada syndrome is associated with 4-20% deaths due to sudden cardiac death, and 20-50% of sudden cardiac death in patients without structural heart disease. Brugada syndrome prevalence is 5 out of 10 000 inhabitants, but this figure should be treated with caution, because for many patients the disease is hidden, thus the prevalence could be higher. There are also geographical differences in prevalence: in Japan Brugada syndrome prevalence in the population is 12/10000 (Hermida, Lemoine, Aoun, Jarry, Rey and Quiret, 2000), while in Europe and North America this prevalence is lower (Antzelevitch, Brugada, Borggrefe et al., 2005).

Brugada syndrome is inherited autosomal dominant (Miyasaka, Tsuji, Yama et al., 2001). For 60% of the patients the disease is sporadic, that is, it is not found in their parents and other relatives (Schulze-Bahr, Eckardt, Paul, Wichter and Breithardt, 2005). In most patients whose Brugada syndrome is hereditary, a mutation in SCN5A gene was found encoding  $\alpha$  subunit of cardiac sodium channel (Chen, Kirsch, Zhang et al., 1998). However, there are more than 100 other gene mutations in the case of Brugada syndrome (Vatta, Dumaine, Varghese et al., 2002). Since there are many mutated genes, it may give rise to heterogeneous ECG findings in this group of patients.

Patients with Brugada syndrome may be asymptomatic, but syncope episodes, polymorphic ventricular tachycardia or ventricular fibrillation during lifetime is observed in up to 42% of Brugada syndrome patients (Brugada J., Brugada R., Antzelevitch, Towbin, Nademanee and Brugada P, 2002; Eckardt, Probst, Smits et al., 2005). Since for a large proportion of asymptomatic patients the diagnosis is not stated and the first episode of the disease is often

fatal, disease manifestation incidence may be higher. It should also be mentioned that the sudden deaths in a group of young people still often remain unexplained. The information about clinical manifestations and prognosis of children with Brugada syndrome is insufficient.

Since ECG changes *per se* do not approve the diagnosis of Brugada syndrome, the provocation tests with sodium channel blockers are used in order to “strengthen” sodium channel dysfunction. The most effective method of treatment in case of Brugada syndrome is ICD implantation and they are implantable for all symptomatic patients. In recent years the studies have been published dealing with radiofrequency catheter ablation (RFCA) performed in patients with Brugada syndrome with an epicardial approach by RFCA applications in the frontal part of the right ventricle outflow tract (Sunsaneewitayakul, Yao, Thamaree and Zhang, 2012). This method seems promising and effective, but not yet recommended in guidelines.

#### **2.4. Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is a disorder characterized by an unexplained left ventricular myocardial hypertrophy, but there is no ventricular cavity dilatation and there is no other heart or systemic disease that could cause ventricular hypertrophy in a given patient. Patients, who are genotypically positive, may be phenotypically negative without overt hypertrophy (American College of Cardiology Foundation, American Heart Association, 2011). The HCM criterion in adults is the maximum left ventricular wall thickness which is greater than 15mm, wall thickness of 13 to 14mm can be regarded as a threshold, especially if it is shown in the family’s medical history (ACCF/AHA, 2011). In children left ventricular wall thickness is considered as increased when it is greater than 2 standard deviations from the mean value (z-score) for a given age, sex and weight.

HCMP is a common genetic cardiovascular disease worldwide (Maron, 2004). Reports from various parts of the world are supported by a similar prevalence of the disease – it is around 0.2 % or 1: 500 in the general population (Zou, Song, Wang et al., 2004).

HCMP is characterized by a myocardial hypertrophy which is inadequate and often asymmetrical. While any part of the left ventricle may be affected, most often there is a hypertrophy of interventricular septum, which can lead to left ventricular outflow tract obstruction. Patients are usually with preserved systolic function with impaired left ventricular filling that causes diastolic dysfunction. HCMP is caused by mutations in the genes encoding sarcomere proteins in myocardium. Jarcho and colleagues reported about the disease-causing gene in the long arm of the 14<sup>th</sup> chromosome encoding the beta heavy chain of cardiac myosin in 1989 (Jarcho, McKenna, Pare, Solomon et al., 1989). In later studies HCMP is linked to at least 15 different genes in at least 6 different chromosomes.

Family HCMP is inherited in autosomal dominant form and about 50 % of subjects with the detected mutation have disease-related changes. The different disease penetrance among family members of the same genetic defect is explained with various modifying individual genes that affect disease expression. Sporadic forms of the disease are associated with spontaneous mutations (Miyake, Berul, Johnsrude, Martin and Windle, n. d.).

HCMP can be found at any age; most commonly in the third decade of life. For the children diagnosed with HCMP, the average age at the moment of diagnosing was 7 years, one third of them being diagnosed before reaching 1 year of age (Miyake, Berul, Johnsrude, Martin and Windle, n. d.).

The studies involving children with HCMP, have shown that the mortality rate of this disease is lower than previously reported, probably due to the fact that the recognition of the disease has improved, allowing to diagnose the disease in less severe cases (Colan, Lipshultz, Lowe, Sleeper, Messere and

Cox, 2007). Overall mortality is about 1 % per year. For infants, if the disease was diagnosed before reaching 1 year of age, the mortality rate is higher. Sudden death is the most common cause of death in children with HCMP. Unfortunately, sudden death may be the first manifestation of the disease even in asymptomatic patients. In children and adolescents with HCMP sudden death occurs frequently when practising sports or during heavy physical exertion. For more than 80% of the individuals with HCMP ventricular fibrillation is the most common arrhythmia that causes sudden death (Miyake, Berul, Johnsrude, Martin and Windle, 2016.). Different mechanisms of palpitations and dizziness are common in children with HCMP who have an elevated pressure gradient of the left ventricular outflow tract. They are reinforced by physical exercise. Dizziness may be increased by hypovolemia, as well as during vagal maneuvers such as rapid getting up or Valsalva maneuver during defecation, which reduces preload and increases the pressure gradient in the left ventricular outflow tract. Dizziness may be related to hypotension and reduced cerebral perfusion due to arrhythmias. Non-persistent arrhythmia episodes are often linked to dizziness and presyncope while persistent arrhythmias are more associated with syncope, collapse and sudden cardiac death. The first diagnostic method in HCMP diagnosis is ECG (ACCF/AHA, 2011).

## **2.5. Wolff–Parkinson–White syndrome (WPW syndrome)**

In 1893 Stanley Kent described the fibers that cross the lateral part of *sulcus atrioventricularis*, believing them to be a normal nodal connection between atria and ventricles (Kent, 1893). Although this interpretation was wrong, he was the first who described the additional conduction pathways between the atrial and ventricular myocardium and these fibers are still called Kent fibers or pathways. In 1930 Wolff, Parkinson and White described the syndrome, which consisted of short PQ interval with bundle branch block in

ECG and paroxysmal tachycardia (Wolf, Parkinson and White, 1930). The authors did not understand the anatomical and electrophysiological nature of their discovery, but the article urged the researchers to carry out further investigations. Modern understanding of WPW syndrome was first described by *Holtzmann* and *Scherf*, mentioning the backward pulse circulation between the atrioventricular connection and the additional pathway (Holtzmann and Scherf, 1932).

Additional pathways are the result of incomplete atrial and ventricular muscle fiber separation during embryogenesis and can be located in different places around the tricuspid and mitral ring (Munger, Packer, Hammill et al., 1993). The prevalence of WPW syndrome is 0.15 to 0.25 %, but may vary depending on gender, population and age (Dunningan, 1986).

## **2.6. The role of ECG screening**

Sudden death at an early age is a traumatic event both for the family and entire community; therefore in recent years the role of ECG in the overall population has been widely discussed in literature, especially regarding children and young people. The discussion is still on about the optimal method and time of investigation for the early determination of sudden cardiac death risk among athletes and the population as a whole. Potential disadvantages of ECG when it is used as a screening method for cardiovascular risk assessment in young people are the following:

- low prevalence of the cardiovascular disease, which can cause sudden death in children and young people;
- low overall risk of sudden death due to this disease in the corresponding population;

- disadvantages of a 12-lead ECG as a screening method for detecting the risk of sudden death ;
- Excessive high population coverage under investigation is required in order to identify potential high risk patients.

However, there is not a wide range of alternatives for the choice of other investigative techniques – echocardiography, which is a widely accepted method for the diagnosis of hypertrophic cardiomyopathy has no diagnostic significance in other major diseases causing sudden cardiac death. Echocardiography and magnetic resonance imaging screening in a wide population is not considered, mainly due to the high-cost, the subjectivity of the wide screening of population and the interpretation of examination results.

Most publications are available about performing ECG before the start of enhanced physical activity among young athletes. The importance of performing ECG among athletes has been widely studied in Italy (Corrado, Basso, Schiavon et al., 2008), the United States of America (Maron, 2012), Israel (Drezner, 2012) and elsewhere.

The main causes of sudden death especially among young athletes are widely described (Maron, 2003; Maron, Doerer, Haas et al., 2009; Maron, Shirani, Poliac et al., 1996; Maron, Haas, Murphy et al, 2014). Hypertrophic cardiomyopathy is in the first place from about 20 diagnoses associated with approximately one third of deaths.

Both the European and US registers have recorded the most sudden deaths cases among football players and basketball players, and there was a difference between the sexes: in men it was observed 9 times more often than in women, while the data on similar problems in children and adolescents are very limited or available just for selected population.

## **2.7. ECG screening in general population**

There have been a few studies on the incidence of sudden cardiac death in young people and children. Sudden cardiac death incidence is 6.6 cases detected in 1 000 000 person years (Atkins, Everson-Stewart, Sears et al., 2009) and 3.2 cases in 100 000 person years in children (Atkins, Everson-Stewart, Sears et al., 2009) and 2.3 cases in 100 000 person years for children and young people population (Meyer L., Stubbs, Fahrenbruch et al, 2012).

There is not a lot of research on ECG screening performed in the general population. The data about the military have been summarised since ECG investigation is mandatory before starting the military service in many countries. In Italy the results of military persons' screening programme were analysed (Nistri, Thiene, Basso et al., 2003). This program was provided for the collection of medical history, physical examination and 12-lead ECG tests. Among the investigated 34 910 people changes were detected in 8%, and those who were undergoing echocardiography examination due to ECG findings, 0.7% were newly diagnosed with hypertrophic cardiomyopathy.

ECG screening programs for school-age children is a rarity – in 1973 in Japan the investigation was laid down by law (history collection, physical and ECG investigation) in the first, seventh and tenth grade pupils (Nistri, Thiene, Basso et al., 2003). Within the framework of this programme, in 2–3 % of children some undiagnosed heart diseases were revealed.

### **3. AIM, TASKS AND HYPOTHESES**

#### **3.1. Aim of the thesis**

The aim of the thesis was to determine the role of electrocardiographic screening and frequency of pathological ECG findings among the first form Latvian pupil population.

#### **3.2. Specific objectives**

1. Perform electrocardiographic investigation in Latvian first form pupil population.
2. Analyse the frequency of abnormal electrocardiographic findings and their character.
3. Develop ECG standard centile tables for the children investigated.
4. Compare the resulting centile tables with those widely used at present.
5. Depending on the pathological ECG findings to perform further investigation to determine the sensitivity of the abnormal electrocardiographic findings.
6. Investigate the importance of electrocardiographic screening in the population of first formclass pupils in Latvia.
7. The standard of normal ECG percentiles in the age group of 7–8 year was developed.

### **3.3. Dissertation hypotheses**

1. ECG is a sufficiently sensitive method for the early diagnosis of certain cardiac diseases, such as WPW syndrome, hypertrophy of separate parts of the heart, inherited cardiomyopathies, etc.
2. Changes in ECG correlate with further findings.
3. 6–9 years of age is most appropriate to carry out ECG screening in asymptomatic individuals.
4. The developed ECG standard percentiles obtained by aggregating the data from a large number of children in Latvia might differ from the tables used so far.
5. ECG screening is significant for hidden heart disease diagnosis in the first form pupil population.

## 4. MATERIAL AND METHODS

Target population was Latvian first form pupils 6–9 years of age. This population was chosen because children at this age usually have not yet manifested life-threatening arrhythmias (they have not experienced enhanced physical and emotional loads), their heart rate already allows for a relatively accurate assessment of ECG, as well as first form pupils are easy to count. A 12-lead ECG investigation was carried out by means of ELI 150c resting electrocardiograph (manufacturer *Mortara Instrument, Inc., Milwaukee, Wisconsin U.S.A.*) for 852 first form pupils in Latvia. As the basis for data processing electrocardiograph measurements taken automatically were chosen, but in case of doubt they were checked visually. Holter monitoring was performed with Holter monitor *Mortara instrument H12+*.

### 4.1. Statistical data processing

In data processing Microsoft Excel 2010 software programme, Pivot Tables and Pivot Charts tools – for the group average comparison and patient sample description were used.

The program SPSS 20 (Statistic Package for Social Science) was used for correlation analysis, for Pearson correlation coefficient calculation between indicators descriptive statistics was used, Student's T-criterion, univariate analysis of variance ANOVA method, Kolmogorov-Smirnov one-sample test, to determine left ventricular mass according to the child's weight and height Z score scale was used.

## 4.2. Data acquisition methods

### 4.2.1. Questionnaire

Primary inspection questionnaire form is shown in Table 4.1.

Table 4.1.

**Primary inspection form**

Name, Surname	Age	The school where examination was performed	Phone Number	Height, weight	Gender	School with Latvian / Russian language
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The following data for each child were collected in schools, where the ECG examination was performed: name, surname (except for 12 children whose parents did not allow to use their children's personal data for the trial, including name and surname), age and the school where examination was performed, parents' phone number, the child's weight, gender as well as the language of instruction at school. Children's health history cards were reviewed to gather information on chronic diseases as well as regular medication they take. Children who were constantly taking medication that could affect the ECG findings were excluded. There were no children with previously known cardiac pathology in the study group.

### 4.2.2. ECG analysis

12-lead ECG was defined as abnormal:

1. Heart rate  $< 65 \times'$  or  $> 140 \times'$ .

2. PQ interval  $< 9$  msec or  $> 17$  msec, atrioventricular conduction disorders.
3. QRS complex electrical axis deviation in the frontal plane  $< -30^\circ$  or  $> 120^\circ$ .
4. Increased QRS complex voltage: S lead  $V_1 + R$  lead  $V_6 > 47$  mm.
5. The left bundle branch block with QRS length  $> 110$  msec.
6. Epsilon wave or isolated QRS complex prolongation  $> 110$  msec lead  $V_1-V_3$ .
7. Adjusted QTc interval (QTc) prolongation  $> 460$  msec.
8. Ventricular premature irritability signs or Delta wave.
9. If something of the above-mentioned is detected in electrocardiographic findings, further action is guided by the presented picture.

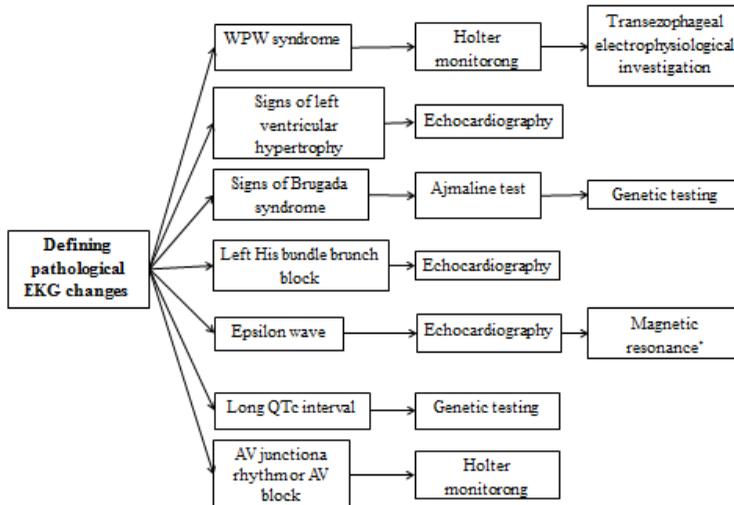


Figure 4.1. **Scheme of further actions in case if pathological ECG changes was detected**

## 5. RESULTS

### 5.1. Demographic indicators

Within the framework of the study 12-lead ECGs were carried out and analyzed in 852 first form pupils in Latvia.

School selection was made randomly, but some role was also played by the fact whether school directors gave their consent to the children investigation. It should be noted, however, that only one school in Jekabpils refused to participate in the study. Excluded from the study were children who constantly were taking medication that could affect the ECG (e.g., inhaled  $\beta$  adrenomimetics). Children's medical records were reviewed in order to exclude those with previously known heart abnormalities that could affect the ECG, but there were no such children.

Among the examined there were 414 boys and 438 girls. Distribution by age and gender is shown in Table 5.1.

Table 5.1.

**Children distribution by age and gender**

Age, years	Girls	Boys
6	14	5
7	283	268
8	140	140
9	1	1
Together	438	414

The average age of the children was 7.31 years ( $\pm 0.51$ ), girls 7.29 years ( $\pm 0.54$ ), boys 7.33 years ( $\pm 0.50$ ). The average height in the studied children was 123.55 cm ( $\pm 8.84$ ), boys 124.44 cm ( $\pm 8.80$ ), girls 122.81 cm ( $\pm 8.63$ ),  $p = 0.06$ . The average weight of the study group was 24.32kg ( $\pm 5.04$ ), girls 23.96kg ( $\pm 5.13$ ), boys 24.83kg ( $\pm 4.96$ ),  $p = 0.058$ . The average body mass

index (BMI) in a study group was 15.82 ( $\pm$  2.12), 27 children were found overweight (body mass index > 22 (esaugu.lv, 2010).

The language of instruction at school was taken into account – in schools with the Russian language of instruction 254 children studied, including 129 girls and 125 boys, in schools with the Latvian language of instruction there were 598 children, including 309 girls and 289 boys. Since in schools with the Latvian language there were more children, groups are different by number. All the children were of the Caucasian race.

## **5.2. ECG analysis**

The following measurements were studied during the ECG analysis: heart rate, PQ interval, QRS complex length, QTc, QRS complex axis, S wave amplitude in lead V1 and the R wave amplitude in lead V5 or V6, whichever was greater. Dental amplitudes were expressed in millimeters, where 1 mm = 0,1 mV.

The average heart rate was 90.55 times per minute ( $\pm$  13.93), girls had statistically significantly higher – 91.52 per minute ( $\pm$  13.52) than boys – 89.54 times per minute ( $\pm$  14.08),  $p = 0.035$ . Heart rate negatively correlated with weight – the higher the weight, the lower HR.

QRS complex width on average was 83.62 msec ( $\pm$  9.04), for girls it was statistically significantly shorter – 82.20 msec ( $\pm$  9.499) than boys 85.18 msec ( $\pm$  8.33),  $p = < 0.0001$ . For children in schools with the Latvian language of instruction QRS width on average was 84.14 msec ( $\pm$  9.42), for children in schools with Russian as the language of instruction – 83.4msec ( $\pm$  8.950). No significant difference between these groups ( $p = 0.38$ ) was found. QRS width correlation with weight was not observed.

QTc on average was 386.93msec ( $\pm 12.40$ ), for girls the average QTc was 386.78msec ( $\pm 12.77$ ) and it was not different from boys – 387.05 msec ( $\pm 12.09$ ),  $p = 0.79$ . For children in schools with the Latvian language of instruction the average QTc interval was 386.26 msec ( $\pm 10.91$ ) and it did not differ from QTc for children in schools with Russian as the language of instruction – 385.68 ( $\pm 10.49$ ),  $p = 0.55$ . QTc interval length correlation with weight was not observed.

QRS complex axis on average was  $70.91^\circ$  ( $\pm 21.19$ ), girls on average had  $71.77^\circ$  ( $\pm 20.29$ ), boys had  $69.85^\circ$  ( $\pm 22.31$ ),  $p = 0.20$ . For children in schools with the Latvian language of instruction the QRS complex axis on average was  $71.72^\circ$  ( $\pm 20.47$ ) and it did not differ from the QRS complex axis for children in schools with Russian as the language of instruction –  $72.36^\circ$  ( $\pm 19.08$ ),  $p = 0.73$ . A negative correlation was observed between the QRS complex axis and weight – the higher the weight, the QRS axis was closer to 0.

S wave amplitude in lead  $V_1$  or  $V_2$  by selecting the highest amplitude, on average was 10.52 mV ( $\pm 4.74$ ), for girls on average it was 10.80 mV ( $\pm 4.67$ ), for boys on average it was 10.25 mV ( $\pm 4.81$ ) and was not statistically different ( $p = 0.99$ ). For children in schools with the Latvian or Russian language of instruction the S wave amplitude in lead  $V_1$  ( $V_2$ ) was not different ( $p = 0.78$ ). S wave amplitude in lead  $V_1$  ( $V_2$ ) did not correlate with weight.

R wave amplitude in leads  $V_5$  or  $V_6$ , choosing a higher amplitude measurements, on average was 17.04 mm ( $\pm 5.33$ ), for girls on average it was 17.12 mm ( $\pm 5.18$ ), for boys on average it was 17,15mm ( $\pm 5.39$ ). For children in schools with the Russian or Latvian language of instruction R wave amplitude in lead  $V_5$  ( $V_5$ ) was not different ( $p = 0.53$ ). R wave amplitude in lead  $V_5$  ( $V_6$ ) had a positive correlation with weight – the higher the weight, the higher the R wave amplitude.

The aggregate of S wave amplitude in lead  $V_1$  and R wave amplitude in leads  $V_5$  or  $V_5$  ( $SV_1 + RV_6$ ) was taken into account to predict the potential of

the left ventricle hypertrophy. Taking into account the literature data,  $RV_6 + SV_1 > 47$  mm was considered as a sign of left ventricular hypertrophy. The average  $RV_6 + SV_1$  was 27.54 mm ( $\pm 7.86$ ), for girls on average it was 27.94 mm ( $\pm 7.65$ ), for boys on average it was 27.39 mm ( $\pm 7.98$ ),  $p = 0.31$ . This figure did not differ between children in schools with the Russian (28.24 mm ( $\pm 8.16$ )), or Latvian (27.54 mm ( $\pm 8.16$ )) language of instruction;  $p = 0.31$ .  $RV_6 + SV_1$  positively correlated with weight – the higher the weight, the higher  $RV_6 + SV_1$  aggregate. In children with  $RV_6 + SV_1 > 47$  mm echocardiographic examination was conducted (see results below Table 5.3.)

### **5.3. ECG findings analysis**

#### **5.3.1. Standard manifestation**

The investigation showed the ECG findings which do not suggest any pathology in children, but in most cases does not constitute the standard for adults – sinus arrhythmia, negative T waves in leads V1–V4, partial bundle branch block, as well as full-right bundle branch block. Taking into consideration the findings mentioned above, further investigation was not conducted due to this change.

Sinus arrhythmia was frequent among the investigated children – it was found in 356 children from 852, that is 42% of children. Sinus arrhythmia was detected in 202 girls and in 154 boys. Sinus arrhythmia occurred more commonly in girls ( $p = 0.044$ ).

Negative T waves in leads V1–V2 were found in 161 children, i.e. – 19 % of children, including 68 girls and 93 boys. This ECG finding is more common in boys ( $p = 0.03$ ).

Negative T waves in leads  $V_1$ – $V_3$  ECG were observed in 61 children i.e. 1.8 % of children, among them in 28 girls and 33 boys. Negative T waves in leads  $V_1$ – $V_3$  between the genders were equally common ( $p = 0.57$ ).

Negative T waves in leads  $V_1$ – $V_4$  in ECG were found in 7 children – 2 boys and 5 girls.

Conduction disorders in the right bundle branch were found in 80 children or 9.4 % of children, including 29 girls and 51 boys. In boys this finding was observed more frequently ( $p = 0.004$ ).

Left bundle front branch block was found in 13 children or 1.5 % of children, out of whom 9 were boys and 4 were girls.

Right bundle branch block was found in 11 or 1.3 % of children, among them 7 were boys and 4 girls.

Distribution of standard manifestation of ECG findings of the studied children is shown in scheme 5.3. It should be noted that different findings could be observed for one and the same child.

### **5.3.2. Pathological ECG findings**

As mentioned above, as a parameter of left ventricular hypertrophy indicator  $SV_1+RV_6$  greater than 47 mV was chosen. An increased  $SV_1 + RV_6$  indicator was found in 11 (1.29%) of the investigated children.

In one girl Epsilon wave was found in leads  $V_1$  and  $V_2$ .

In 8 children (4 girls and 4 boys) ECG showed rhythm source migration in atria or rhythm from the bottom of the atrium.

In 1 child signs of an additional conduction pathway were found.

Left bundle branch block, prolonged QTc interval or signs of Brugada syndrome were not identified in any of the children.

## 5.4. ECG finding correlation with further examinations

### 5.4.1. Echocardiography examination results

In 11 children, left ventricular hypertrophy was found on ECG. From these children the parents of one child did not give the consent for further investigation. ECG findings and echocardiography data are shown in Table 5.2.

Table 5.2.

#### ECG and echocardiography investigation results in children with ECG criteria of left ventricular hypertrophy

No	SV <sub>1</sub>	R V <sub>6</sub>	SV <sub>1</sub> +R V <sub>6</sub>	Left ventricular posterior wall, mm	Interventricular septum, mm	Left ventricular mass, g	Left ventricular mass, Z score	Remarks
1.	23	25	48	5	5	71.4	-0.34	
2.	29	19	48	6	6	85.28	0.76	
3.	15	39	54	6	7	59.28	-2.15	
4.	28	22	50	6	7	85.8	0.2	The patient was discovered coarctation of aorta
5.	29	20	49	5	6	45.5	-1.79	
6.	23	25	48	4	6	44.46	-3.96	
7.	9	39	48	5	6	64.89	-1.04	
8.	11	42	53	5	7	55.62	-1.63	
9.	9	44	54	7	7	53.82	-0.09	
10.	21	31	52	7	8	98.7	1.41	

Table 5.2. displays the main echocardiographic features of left ventricular hypertrophy (EhoKG) criteria – left ventricular posterior wall

thickness and interventricular septum thickness are direct echocardiographic measurements. Left ventricular mass was calculated by multiplying the left ventricular mass in grams/m<sup>2</sup> of body surface area by body surface area. *Z score* is a scale that is taken into account in children's echocardiography in determining whether left ventricular mass corresponds to the child's height and weight. In adult echocardiographic determination of left ventricular mass there are certain standards to follow, but for children it is not possible because a growing organism is investigated. The increase in the child's heart and left ventricular mass takes place with age, but, for example, in the case of aortic stenosis left ventricular mass grows faster. Therefore, it is difficult to determine whether a child's heart weight gain is adequate and corresponds to the average margin. In addition, it is also necessary to identify the magnitude of the deviation. *Z score* determines how many standard deviations above or below the average size of the defined heart chamber the size is. If according to the *Z score* left ventricular mass is 2 or more, it means that the scores in the patient are over 98<sup>th</sup> percentile compared with children with the same weight and height. If according to the *Z score* left ventricular mass is - 2 or less, it means that the index of patient is under 2<sup>nd</sup> percentile.

As it can be seen in Table 5.2., in none of the children who were suspected for left ventricular hypertrophy, this diagnosis was not confirmed, but in one of them an undiagnosed coarctation of aorta was discovered and operational aortic correction was made.

In the child, who was found with Epsilon wave in leads V<sub>1</sub> and V<sub>2</sub>, echocardiographically right ventricle arrhythmogenic dysplasia diagnosis was not confirmed.

## **5.4.2. Holter monitoring results**

When Holter monitoring a child with additional conduction pathway signs in ECG, WPW phenomenon turned out to be transient and resolved with an increased heart rate  $> 90 \times ' ,$  respectively, it was clinically insignificant.

In children who had AV connection rhythm in ECG, Holter monitoring recorded rhythm source migration in atria till the AV connection with a normal average heart rate and the normal increase in heart rate during exercise.

## **5.5. ECG compliance with percentile**

As mentioned in the literature review so far ECG percentile standards have been used in ECG evaluation that have been identified during the investigation of a relatively small number of children in the relevant age group. Since the literature does not mention such a large group of children that were investigated in this study, it was decided to compare the commonly used ECG standard percentile to the studied group performance. Analysing the studied children's age, it became clear that the 7 and 8-year-olds were the most widely represented – 551 and 280 respectively. The children who were 6 and 9 yearsold were also included in the study – 19 and 2 respectively. Since in the 6- and 9-year-old children's group the ECG parameters differed (however, the number of children in this group was significantly less), these children were not included in the overall analysis. Analysing the remaining group of children, each indicator was set at the 5<sup>th</sup>, the average and the 95<sup>th</sup> percentile. The estimated percentiles are shown in Table 5.3.

Table 5.3.

**ECG norm percentiles estimated in the research for the investigated age**

	95 <sup>th</sup> percentile	50 <sup>th</sup> percentile	5 <sup>th</sup> percentile
Heart rate / min	115	90( $\pm$ 12.36)	70
PQ interval, msec	160	130( $\pm$ 14.81)	106
QRS complex, msec	97	83( $\pm$ 7.16)	71
OTc interval, msec	410	381( $\pm$ 15.28)	355
QRS axis, °	96	71( $\pm$ 17.72)	31
S V <sub>1</sub> , mm	19	10( $\pm$ 4.32)	3
R V <sub>6</sub> , mm	26	17( $\pm$ 4.67)	8

Table 5.4. displays up till now used ECG measurement standards in the investigated age.

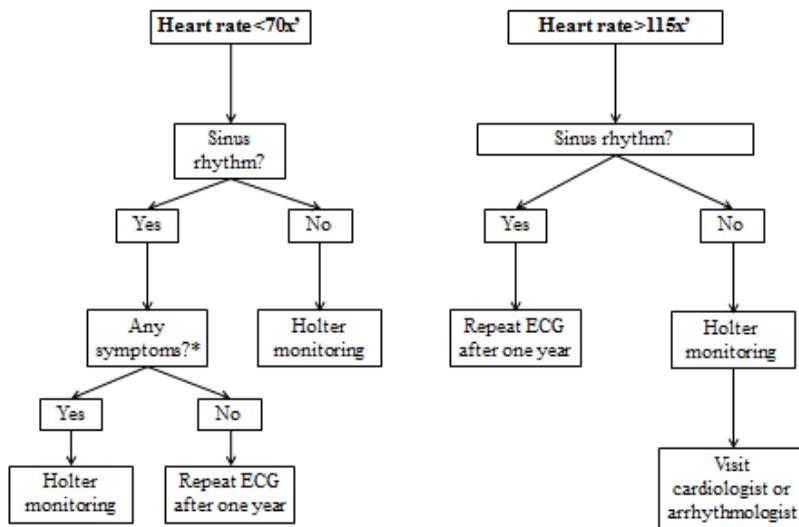
Table 5.4.

**ECG percentiles up till now used in the investigated age**

	95 <sup>th</sup> percentile	50 <sup>th</sup> percentile	5 <sup>th</sup> percentile
Heart rate / min	119	94	74
PQ interval, msec	152	131	110
QRS complex, msec	97	86	74
OTc interval, msec	450	420	390
QRS axis, °	93	66	34
S V <sub>1</sub> , mm	13,5	7	1
R V <sub>6</sub> , mm	23	15	8

Since the percentiles cannot be compared directly, in order to determine whether the obtained percentile standard differs from the one used up till now, Fisher's F-criterion of two samples variance comparison was used. Differences were found between the calculated centile dispersion and the dispersion of the up till now used standards for the population studied in the following parameters: heart rate, PQ interval, QRS width, QRS axis, S wave amplitude in lead V<sub>1</sub> and the R wave amplitude in lead V<sub>6</sub>.

### 5.5. Complex of algorithms for further action depending on the 7-8 year-old child's ECG findings



\*syncope, dizziness

Figure 5.1. Tactics algorithm on the basis of heart rate in children aged 7 to 8 years

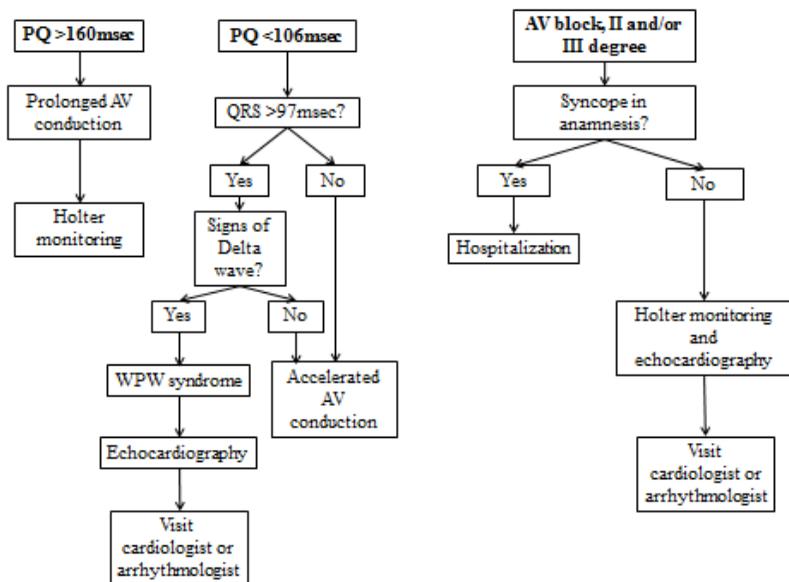


Figure 5.2. Tactics algorithm on the basis of the PQ interval and atrioventricular conduction abnormalities in children aged 7 to 8 years

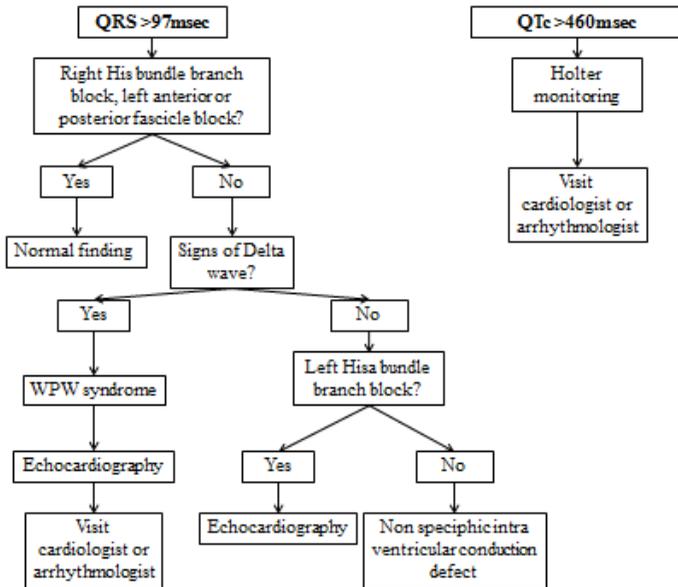
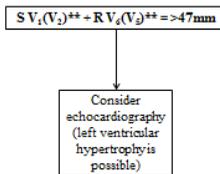


Figure 5.3. Tactics algorithm on the basis of the width of the QRS complex and QT interval length for children aged 7 to 8 years



\*\*chose the biggest amplitude

Figure 5.4. Tactics algorithm on the basis on the sum of amplitude of the S wave in lead V1 (V2) and the R wave in lead V6 (V5) for children aged 7 to 8 years

## 6. DISCUSSION

With the electrocardiographic investigation of first form pupils in Latvia and with the studied population which was more than reviewed in the available literature so far, it was possible to accurately determine more appropriate centile values of the most often measured ECG parameters under current Latvian conditions. Most of the data obtained were different from previously accepted standards. As a certificate of health is required for children at the beginning of the school year, within the process of electrocardiographic investigation the idea of using the ECG readings rules developed in the current thesis as well as the further action algorithm should be considered based on the ECG findings developed in this work.

Taking into account the children's ECG limitations imposed by the cardiac anatomical changes with age (e.g., QRS axis turnover, often occurring negative T waves in the right and precordial chest leads, higher QRS complex amplitudes etc.), as well as other children's ECG differences from adult ECG (more often sinus arrhythmia and rhythm spring migration fast, differences in PQ interval length), it was not purposeful to focus on a wide range of targeted use of electrocardiographic investigation at that age, as health examinations for children starting school are performed by the general practitioners, who are usually not specialized in pediatrics. The resulting standard indicators of most frequently used parameters (SD, PQ, QRS, QTc) facilitate electrocardiographic investigation in 7–8 year old children and allow a safer definition of pathological findings. The introduction of ECG interpretation algorithm in 7–8 year olds would improve the early diagnosis of latent cardiac diseases in the general medicine practice in all of Latvia. By performing electrocardiographic screening of all 7–8 year olds and processing the data in a centralized way, it would be possible to get an idea of the spread of primary cardiomyopathy and other latent pathology (e.g. WPW syndrome) in Latvia and to start an early

prevention of possible complications. It can be noted that, although the cost of electrocardiographic investigation is not high, the necessity for further investigations would require both additional materials and human resources, but early detection of cardiac diseases, especially if they are associated with a potential risk of sudden death at an early age, in the long run would certainly be economically efficient.

Analysing gender differences of ECGs, statistically significant difference was determined in heart rate for girls and boys: for girls it was higher. These differences are probably due to the fact that girls in a pre-school age are doing less physical activity than boys. The anxiety before the examination could also be a reason. The width of QRS complex was also statistically significantly different: in girls QRS complex in average was wider than in boys. So far gender differences of ECGs have not been widely discussed in scientific literature.

As in literature the ECG differences related to race are described, the author of the thesis compared ECG findings in children who studied in schools with the Latvian or Russian language of instruction. Statistically significant differences were not detected. It should be noted that children in all schools were Caucasians, and the fact that the division only by language of instruction in school is imprecise in terms of definition of nationality. The surveyed children were at the age when they could not declare their nationality yet, and such a distinction is very conditional in the demographic situation in Latvia. The research results show that the resulting standard performance is attributable to the first form pupils in schools with the Russian as well as Latvian language of instruction.

Left ventricular hypertrophy criteria considering the child's anatomical features (thin chest wall, heart rotation with age) is still unclear. The study used the criteria recommended by the American Heart Association  $S V_1 + R V_6 > 47$  mm, but in none of the children in echocardiographic examination left

ventricular hypertrophy was detected. In one of the children previously undiagnosed coarctation of aorta was found, but also in this case, the left ventricular mass was not increased. Since the adopted criterion  $S V_1 + R V_6 > 47\text{mm}$  was not sufficiently sensitive there is a need for further ECG and echocardiographic studies in a sufficiently large children population.

None of the children in the study had ECG signs of primary cardiomyopathy. Since these abnormalities are rare, the studied population, though presumably until now one of the largest groups of children investigated with ECG at this age, however, was too small to detect them. It is necessary to continue the investigations in this area in order to draw conclusions about the prevalence of primary cardiomyopathy in Latvia and the frequency of more common gene mutations.

For children who had a rhythm source migration in ECG and even rhythm of atrioventricular connection, Holter monitoring was recorded, but there were no significant pauses and bradycardia, which indicates a good prognosis of the ECG findings in this case. It is possible that it disappears with age. For the approval of this assumption further investigation of children should be performed.

For children with heart rate greater than accepted standards, but provided that the heart rate source was the sinus node, Holter monitoring was not performed, assuming that the higher heart rate is associated with the children's emotional response to the ECG recording fact as to any other medical manipulation. Possibly, Holter monitoring should be considered also in these cases.

In terms of the usefulness of ECG screening for children starting school a number of considerations and limitations should be taken into account. Sensitivity and therefore the impact on the value of ECG as a screening method is influenced by the technical quality of the recorded ECG, the competency of the analyser to identify potentially important markers of sudden cardiac death

and the skills in the ECG analysis of the children in the investigated age. The utility of ECG method in diagnosis of channelopathies and cardiomyopathies depends on the assay sensitivity and specificity. Even if the ECG is adequately interpreted, the fact, that the diagnoses associated with sudden death in the surveyed population are rare and fatal events among these children are even rarer, must be taken into account. However, there is no other more effective method in the screening investigation of channelopathies (extended or shortened QT syndrome and Brugada syndrome), additional conduction pathways and left ventricular hypertrophy. That is why the early detection of diagnosis would allow a timely launch of the treatment and/or prevention.

ECG as a screening method has some technical limitations. By placing the chest electrodes over inaccurate intercostal spaces, which often happens when recording ECG in children, one can get wrong readings (for example, change of S wave amplitude in lead V1 and V2, R wave progression between the leads, changes in ST segment and the appearance of R'). In this study, ECG was carried out with the same ECG apparatus and the recording was carried out by the same person - the author of the research. Also the interval measurement could be problematic using ECG as screening. The accuracy of modern ECG recording apparatuses is very high, but it is necessary to check the automatic measurements. Especially problematic is the QTc interval setting, because it depends on the lead where the QT interval is measured, and also on the ECG recording quality, which in a given age of the screened population is not always optimal.

For sudden cardiac death risk screening the history data collection and physical examination should also be performed, although partly it is already being done in Latvia. However, before the introduction of electrocardiographic investigation of the children starting school in Latvia certain considerations should be taken into account, such as: who will interpret the ECG and what the further action will be when certain abnormalities are found. The most

disputable issue is the prohibition of physical activities, especially for the children who are engaged in more intensive sports activities. In addition, further investigations (e.g. intracardial electrophysiological investigation) would require parental consent – without which the ECG investigation loses its significance.

## 7. CONCLUSIONS

1. 12-lead ECG investigation performed in 852 first form pupils in Latvia included a representative and informative study population group which allowed the statistical analysis to be performed. Among the investigated children there were 438 girls (51.4%) and 414 boys (48.6%).
2. The identified electrocardiographic changes correlated with the incidence of ECG phenotypic changes in the general population:
  - a. Increased  $SV_1+RV_6$  indicator was found in 11 (12.9 in 1000) of the studied children.
  - b. One child (1.2 in 1000) had Epsilon wave in leads V1 and V2.
  - c. One child (1.2 in 1000) had WPW syndrome.
  - d. In 14 children (16.4 in 1000) the ECG showed atrial rhythm source migration to the AV connection.
3. The identified electrocardiographic abnormalities and their specific morphological changes were not approved by further deeper investigations in accordance with the algorithm, which confirms that the indicator used did not show sufficient sensitivity to that pathology.
4. In the children who had AV connection rhythm in ECGs, Holter monitoring recorded atrial rhythm source migration to the AV connection with a normal average heart rate and a normal increase in heart rate during exercise, suggesting that for the studied children this finding is permissible.
5. The investigated group of children did not have electrocardiographic signs of family cardiomyopathy (PQTS and Brugada syndrome) which suggests that the number of children included in the study however was too small for the diagnosis of this pathology.
6. As a result of the research electrocardiography standard centile tables were developed for the children of the corresponding age group and the

acquired ECG centile standards are different from those previously used both in absolute figures and also by variance.

7. The algorithm for further action that was developed may also be useful in clinical practice in ECG interpretation and for further action for family doctors and other professionals caring for children aged 6 to 8 years.
8. The calculated centile standards allowed the author to develop practical recommendations and algorithms for the evaluation of the ECGs of the first form pupils.
9. Although the proportion of abnormal ECG findings in the studied population was small, ECG screening of a wider population could detect latent heart diseases earlier. These ECGs could be used for the person concerned to compare them with the ones performed later in their lives. The complex of algorithms and practical recommendations created within the framework of the thesis are targeted to use not only for general practice doctors, but also for sports school physicians in the work with young athletes at the appropriate age.

## LITERATURE SOURCES

1. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: BreakA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. – *J Am Coll Cardiol*, 2011. 58 (25): e212–e260.
2. AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram: Part V: Electrocardiogram Changes Associated With Cardiac Chamber Hypertrophy A Scientific Statement From the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009; 53(11):992-1002. doi:10.1016/j.jacc.2008.12.015
3. Akiba T, Nakasato M, Sato S, et al: Angiographic determination of left and right ventricular volumes and left ventricular mass in normal infants and children. *Tohoku J Exp Med* 1995; 177: 153
4. Antzelevitch C., Brugada P., Borggreffe M. et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. – *Circulation*, 2005. 111: 659–670.
5. Atkins D. L., Everson-Stewart S., Sears G. K. et al. Epidemiology and outcomes from out-of-hospital cardiac arrest in children: the Resuscitation Outcomes Consortium Epistry-Cardiac Arrest. – *Circulation*, 2009. 119: 1484–1491.
6. Bardai A., Berdowski J., van der Werf C. et al. Incidence, causes, and outcomes of out-of-hospital cardiac arrest in children: a comprehensive, prospective, population-based study in the Netherlands. – *J Am Coll Cardiol*, 2011. 57: 1822–1828.
7. Brugada J., Brugada R., Antzelevitch C., Towbin J., Nademanee K., Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. – *Circulation*, 2002. 105: 73–78.
8. Chen Q., Kirsch G. E., Zhang D. et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. – *Nature*, 1998. 392: 293–296.
9. Colan S. D., Lipshultz S. E., Lowe A. M., Sleeper L. A., Messere J., Cox G. F. et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. – *Circulation*, Feb 13 2007. 115 (6): 773–781.
10. Corrado D., Basso C., Schiavon M. et al. Pre-participation screening of young competitive athletes for prevention of sudden cardiac death. – *J Am Coll Cardiol*, 2008. 52: 1981–1989.
11. Davignon A, Rautaharju P, Boisselle E, et al Normal ECG standards for infants and children. *Ped Cardiol* 1979; 1: 123

12. Drezner J. A. Standardised criteria for ECG interpretation in athletes: a practical tool. – *Br J Sports Med*, 2012. 46 (suppl 1): i6–8.
13. Dunningan A. Developmental aspects and natural history of preexcitation syndromes. In: Benditt D. G., Benson D. W. Jr (eds) *Cardiac preexcitation syndromes: origins, evaluation and treatment*. – Boston, Martinus Nijhoff Publishing, 1986. pp 21–29.
14. Eckardt L., Probst V., Smits J. P. P. et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. – *Circulation*, 2005. 111: 257–263.
15. Emery JL, Mithal A: Weights of cardiac ventricles at and after birth. *Br Heart J* 1961; 23: 313
16. H.C.Lue *ECG in the Child and Adolescent* Blackwell Futura, 2006.
17. Hermida J. S., Lemoine J. L., Aoun F. B., Jarry G., Rey J. L., Quiret J. C. Prevalence of the Brugada syndrome in an apparently healthy population. – *Am J Cardiol*, 2000. 86: 91–94.
18. Holtzmann M., Scherf D. Über Elektrokardiogramme mit verkürzter Vorhof-Kammer Distanz und positiven P-Zacken. – *Z Klin Med*, 1932. 121: 404–410.
19. <http://esaugu.lv/site/30208>
20. Jarcho J. A., McKenna W., Pare J. A., Solomon S. D., Holcombe R. F., Dickie S. et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. – *N Engl J Med*, Nov 16 1989. 321 (20): 1372–1378.
21. Kent A. F. S. Researches on the structure and function of the mammalian heart. – *J Physiol*, 1893. 14: 233.
22. Krous H. F., Beckwith J. B., Byard R. W., Rognum T. O., Bajanowski T., Corey T., Cutz E., Hanzlick R., Keens T. G., Mitchell E. A. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. – *Pediatrics*, 2004. 114: 234–238. [PubMed].
23. Maron B. J. Counterpoint: mandatory ECG screening of young competitive athletes. – *Heart Rhythm*, 2012. 9: 1646–1649.
24. Maron B. J. Hypertrophic cardiomyopathy: an important global disease. – *Am J Med*, 2004, 116: 63–65.
25. Maron B. J. Sudden death in young athletes. – *N Engl J Med*, 2003. 349: 1064–1075.
26. Maron B. J., Doerer J. J., Haas T. S. et al. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. – *Circulation*, 2009. 119: 1085–1092.
27. Maron B. J., Haas T. S., Murphy C. J. et al. Incidence and causes of sudden death in U.S. college athletes. – *J Am Coll Cardiol*, 2014. 63: 1636–1643.
28. Maron B. J., Shirani J., Poliac L. C. et al. Sudden death in young competitive athletes: clinical, demographic, and pathological profiles. – *JAMA*, 1996. 276:199–204.
29. Merri M., Benhorin J., Alberti M., Locati E., Moss A. J. Electrocardiographic quantitation of ventricular repolarization. – *Circulation*, 1989. 80: 1301–1308.
30. Meyer L., Stubbs B., Fahrenbruch C. et al. Incidence, causes, and survival trends from cardiovascular-related sudden cardiac arrest in children and young adults 0 to 35 years of age: a 30-year review. – *Circulation*, 2012. 126: 1363–1372.

31. Miyake C. Y., Berul C. I., MD, Johnsrude C., MD, Martin A., MD, Windle M. L. PharmD Pediatric Hypertrophic Cardiomyopathy <http://emedicine.medscape.com/article/890068-overview#showall>
32. Miyasaka Y., Tsuji H., Yamada K. et al. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. – *J Am Coll Cardiol*, 2001. 38: 771–774.
33. Moss A. J., Robinson J. L. The long QT syndrome. – *Circulation*, 2002. 105: 784–786.
34. Moss A. J., Robinson J. L. The long QT syndrome. – *Circulation*, 2002. 105: 784–786.
35. Munger T. M., Packer D. L., Hammill S. C., Feldman B. J., Bailey K. R., Ballard D. J., Holmes D. R. Jr, Gersh B. J. A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted County, Minnesota, 1953-1989. – *Circulation*, 1993. 87: 866–873.
36. Nemeč J, Hejlik JB, Shen WK, Ackerman MJ: Catecholamine-induced T-wave lability in congenital long QT syndrome: a novel phenomenon associated with syncope and cardiac arrest. *Mayo Clin Proc* 2003, 78:40-50.
37. Nistri S., Thiene G., Basso C. et al. Screening for hypertrophic cardiomyopathy in a young male military population. – *Am J Cardiol*, 2003. 91: 1021–1023.
38. Onat T, Ahunbay G: Regression of right ventricular dominance in the electrocardiogram after birth: a longitudinal follow-up of a healthy cohort from birth to 3 years. *Pediatr Cardiol* 1998; 19: 197
39. Rao PS, Thapar MK, Harp RJ, et al: Racial variations in electrocardiograms and vectorcardiograms between black and white children and their genesis. *J Electrocardiol* 1984; 17: 239
40. Rao PS, Thapar MK, Harp RJ, et al: Racial variations in electrocardiograms and vectorcardiograms between black and white children and their genesis. *J Electrocardiol* 1984; 17: 239
41. Rao PS: Racial differences in electrocardiograms and vectorcardiograms between black and white adolescents. *J Electrocardiol* 1985; 18:
42. Rashba E. J., Zareba W., Moss A. J., Hall W. J., Robinson J., Locati E. H., Schwartz P. J., Andrews M. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS Investigators. – *Circulation*, 1998. 97: 451–456.
43. Rautaharju PM, Zhou SH, Calhoun HP, et al: Ethnic differences in ECG amplitudes in North American white, black, and Hispanic men and women. Effect of obesity and age. *J Electrocardiol* 1994; 27: 20
44. Rivenes SM, Colan SD, Easley KA, et al Usefulness of the pediatric electrocardiogram in detecting left ventricular hypertrophy: results from the Prospective Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P2C2 HIV) multicenter study. *Am Heart J* 2003; 145: 716
45. Schulze-Bahr E., Eckardt L., Paul M., Wichter T., Breithardt G. Molecular genetics of the Brugada syndrome. In: Antzelevitch C, Brugada P, editors. *The Brugada Syndrome: from Bench to Bedside*. 1st ed. – Blackwell Publishing, 2005. p. 42–51.
46. Schwartz P. J., Priori S. G., Spazzolini C., Moss A. J., Vincent G. M., Napolitano C., Denjoy I., Guicheney P., Breithardt G., Keating M. T., Towbin J. A., Beggs A.

- H., Brink P., Wilde A. A., Toivonen L., Zareba W., Robinson J. L., Timothy K. W., Corfield V., Wattanasirichaigoon D., Corbett C., Haverkamp W., Schulze-Bahr E., Lehmann M. H., Schwartz K., Coumel P., Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. – *Circulation*, 2001. 103: 89–95.
47. Schwartz P. J., Stramba-Badiale M., Segantini A., Austoni P., Bosi G., Giorgetti R., Grancini F., Marni E. D., Perticone F., Rosti D., Salice P. Prolongation of the QT interval and the sudden infant death syndrome. – *N Engl J Med*, 1998. 338: 1709–1714.
  48. Stramba-Badiale M., Crotti L., Goulene K., Pedrazzini M., Mannarino S., Salice P., Bosi G., Nespoli L., Rimini A., Gabbarini F., Rosati E., Schwartz P. J. Electrocardiographic and genetic screening for long QT syndrome: results from a prospective study on 44,596 neonates. – *Circulation*, 2007. 116 (Abstr Suppl): II377.
  49. Sunsaneewitayakul B., Yao Y., Thamaree S., Zhang S. Endocardial Mapping and Catheter Ablation for Ventricular Fibrillation Prevention in Brugada Syndrome. – *Journal of Cardiovascular Electrophysiology*, Vol 23, Nov 2012. 10–16.
  50. Tanaka Y., Yoshinaga M., Anan R. et al. Usefulness and cost effectiveness of cardiovascular screening of young adolescents. – *Med Sci Sports Exerc*, 2006.38: 2–6.
  51. Vatta M., Dumaine R., Varghese G. et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. – *Hum Mol Genet*, 2002. 11: 337–345.
  52. Wilde A. A. M., Antzelevitch C., Borggreffe M. et al. Proposed diagnostic criteria for the Brugada syndrome. – *Eur Heart J*, 2002. 23: 1648–1654.
  53. Wolf L., Parkinson J., White P. Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia. – *Am Heart J*, 1930. 5: 585–704.
  54. Zou Y., Song L., Wang Z. et al. Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. – *Am J Med*, 2004. 116: 14–18.

## PUBLICATIONS ON SCIENTIFIC THEME

1. Kalējs O., Lāriņš V., **Jubele K.**, Šipačovs P., Rudzītis A., Rimbenieks J., Černovska B., Lejnieks A. Elektrokardiogrāfijas loma agrīnā dzīvību apdraudošo aritmiju atpazīšanā sportistiem. – RSU Zinātniskie raksti, 2010. 162.–177.lpp.
2. **Jubele K.**, Šipačovs P., Vikmane M., Kalējs O., Lejnieks A. Pagarināta QT sindroma izsauktas kambaru aritmijas 11 gadus vecam zēnam, kuram iepriekš tika ārstēta epilepsija. – RSU Zinātniskie raksti, 2011. 183.–189.lpp.
3. **Jubele K.**, Knipše A., Šešunačeva O., Buļš A., Kalējs O., Lejnieks A. Patoloģiskās elektrokardiogrāfiskās atrades biežums un EKG atbilstība līdz šim pieņemtajām normām pirmās klases skolnieku populācijā. – RSU Zinātniskie raksti, 2014. 172.–182.lpp.
4. Rozenštoka S., Lāce A., **Jubele K.** Analyses of functional abilities of the body and metabolic processes for participants of public sports and professional sportsmen. – RSU Zinātniskie raksti, 2010. 170.–179.lpp.
5. **Jubele K.**, Šipačovs P., Vikmane M., Maca A., Lejnieks A., Kalejs O. Long QT syndrome induced ventricular arrhythmias and diagnostic problems in children. – J Interv Card Electrophysiol, 2011. 30; 87–198. P 180–181.
6. Kalejs O., **Jubele K.**, Vikmane M., Šipacevs P., Nesterovics N., Lejnieks A. Intrahospital arrhythmias – who are we now and what we can do? Proceedings of the Latvian Academy of sciences. 2008. vol 62, number 4/5; S71–S76.

## Reports in international congresses and conferences on the topic

1. **Jubele K.**, Kalējs O., Šipačovs P., Lejnieks A. Pirmais ģenētiski apstiprinātais iedzimta pagarināta QT intervāla sindroma gadījums Latvijā. – RSU Zinātniskā konference. *Tēzes*. 2010. 84.lpp.
2. **Jubele K.**, Vikmane M., Rudzītis A., Zabunova M., Židens J., Mintāle I., Kalējs O., Lejnieks A. Elektrokardiogrāfijas informatīvā nozīme dažādu sirds patoloģiju agrīnā diagnostikā jauniešiem. – RSU Zinātniskā konference. *Tēzes*. 2011. 116.lpp.
3. **Jubele K.**, Lejnieks A., Kalējs O., Knipše A., Šešunačeva O., Buļš A. Patoloģiskās elektrokardiogrāfiskās atrades biežums un tās korelācija ar tālākiem izmeklējumiem pirmās klases skolēnu populācijā Latvijā. – RSU Zinātniskā konference. *Tēzes*. 2014. 107.lpp.
4. **Jubele K.**, Vikmane M., Rudzītis A., Zabunova M., Berzina M., Zidens J., Mintale I., Kalejs O., Lejnieks A., Erglis A. Informativity on surface ECG in early detection of different cardiac pathology in children. // *Medicine* 2011. Nordic – Baltic Congress of Cardiology. p.88.
5. **Jubele K.**, Vikmane M., Rudzītis A., Zabunova M., Berzina M., Zidens J., Kalejs O., Lejnieks A. Informative Role of ECG in Diagnostics of Different pathologies in Adolescents. // *The 11th International Dead Sea Symposium*. 2012. p.148.
6. Kalejs O., Vamze J., Zvaigzne L., Rudzītis A., Mintale I., Zabunova M., **Jubele K.**, Lejnieks A., Erglis A. Sudden Death in Young - Causes and Morphological Finding: Data from Centre for Disease Prevention and Control of Latvia, 2011. Nordic – Baltic Congress of Cardiology. 2013.
7. **Jubele K.**, Knipse A., Sesunaceva O., Buls A., Kalejs O., Lejnieks A. Incidence of pathological electrocardiographic findings and accordance of those with accepted normal ranges in the population of first grade pupils.

*Tēzes.* Eiropas Sirds Ritma asociācijas (EHRA) kongress 2015. Europace. 2015.

8. **K. Jubele.** Early ECG screening in pupils – pro and contra. V Baltic heart failure meeting and arrhythmias Baltica 2016. Oral presentation.