Diagnostics in Cardiology and Grown-Up Congenital Heart Disease: GUCH

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INTERNATIONAL SCIENTIFIC SYMPOSIUM DIAGNOSTICS IN CARDIOLOGY AND GROWN-UP CONGENITAL HEART DISEASE (GUCH)

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AKADEMIJA NAUKA I UMJETNOSTI BOSNE I HERCEGOVINE
АКАДЕМИЈА НАУКА И УМЈЕТНОСТИ БОСНЕ И ХЕРЦЕГОВИНЕ
ACADEMY OF SCIENCES AND ARTS OF BOSNIA AND HERZEGOVINA

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Sarajevo, 15th of April, 2021

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Editor
Senka Mesihović-Dinarević

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INTRODUCTION

Cardiovascular medicine is an area of clinical practice with a continually rapid expansion of knowledge, guidelines, best practices and new technology in adult cardiovascular medicine as well as in paediatric cardiology medicine. Cardiovascular diseases are the leading cause of mortality in the world and cause major costs for the health sector and economy. The majority of CVDs can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diets and obesity, physical inactivity and harmful use of alcohol, using population wide strategy.

World Heart Federation established **the World Heart Day** in 2000 as an annual global observance, to educate people about cardiovascular disease and main methods of its prevention and changes in lifestyle to avoid any cardiovascular diseases, such as heart attack, stroke, heart failure and any other condition related to the same. World Heart Day aims at raising awareness of cardiovascular disease (CVD). World Heart Day is celebrated on 29th September of every year. It is aimed at drawing people's attention to heart illness and the range of associated health issues.

World Heart Day activities and events are organized by the World Heart Federation in collaboration with international and local non-profit governmental and non-governmental organisations. They include: screenings, lectures, public talks, sporting events, concerts, marathons, walks, fitness sessions, exhibitions and science fairs. Some landmarks, monuments, and famous buildings choose to go red on this day as an expression of cardiovascular disease awareness.

Each year, a new theme for the day is selected, and participants are encouraged to link their events to the current year's theme.

A systematic approach to control of cardiovascular diseases is necessary, with the aim of integration into modern European and global medical trends, which would result in a reduction of morbidity and mortality from cardiovascular diseases.

It is necessary to continue monitoring the risk factors for the development of cardiovascular diseases, starting from the fetal period to adulthood. The proactive role of the healthcare system in digital health as a support to cardiovascular health in Europe, is included in the current action plan of the European Society of Cardiology. The future is focused on the digital transformation of healthcare and the need for efficient and safe innovation in order to improve the efficiency of health practices, and thus by improving the diagnosis of preventable diseases ultimately prevent cardiac diseases. Successful implementation requires multidisciplinary approaches, from mass dissemination of recommendations through public health education programs directly in the field to clinical treatments for patients. All this requires the involvement of numerous actors, from the strategic to the operational level of management within the healthcare system in the country.

Cardiovascular imaging indices have a significant impact on the prevention, diagnosis, and treatment of cardiac diseases. Advanced imaging technologies have dramatically improved our ability to detect and treat cardiovascular disease at an early stage. Multimodality imaging techniques - echocardiogram, cardiac computerized tomography, magnetic resonance imaging, simulation 3D models, artificial intelligence - are being used more frequently as their utility is better appreciated. Primary care clinicians are challenged to optimally manage a multitude of diseases involving the cardiovascular system including the heart failure, arrhythmias and the circulation affected by abnormal cholesterol metabolism and hypertension.

Coronavirus disease 2019 /COVID-19/ exerts an unprecedented global impact on public health and health care delivery. Patients with cardiovascular (CV) risk factors and established CVD represent a vulnerable population when suffering from COVID-19, and have an increased risk of morbidity and mortality.

The presented novelties in cardiovascular medicine, including fresh diagnostic guidelines for COVID-19 in children and adults, needs to be incorporated into the medical flows of healthcare in Southeast Europe, to apply diagnostic-therapeutic algorithms for cardiovascular diseases; make professional promotion of systemic interventions, which also improves health in accordance with good medical practice and evidence-based medicine and guidelines of the World Health Organization and the European Union.

As a part of lifelong learning process for all professionals in cardiovascular medicine, the imperative is to have continuity of reviewing

novelties along with research results, in order to treat patient according to best practices and evidence-based medicine, especially on this journey through corona pandemic.

Board for Cardiovascular Pathology of the Department of Medical Sciences of the Academy of Sciences and Arts of Bosnia and Herzegovina

Organisation of health protection represents a reflection of a country's stage of development.

In the past years the Board for Cardiovascular Pathology has organized the following Symposiums, which resulted in publications published by the Academy of Sciences and Arts of Bosnia and Herzegovina

- Symposium: "I Work with Heart", ANUBiH, 2010.
- International Symposium: "Pulmonary Arterial Hypertension", ANUBIH, Book 39, 2011.
- Symposium: "Risk Factors for the Emergence of Cardiovascular Diseases", ANUBiH, Book 40, 2011.
- Symposium: "Innate Heart Anomalies", ANUBiH, Book 42, 2012.
- International Symposium: "Perspectives in Paediatric Cardiology", ANUBiH, Book 43, 2012, English edition.
- Symposium: "Heart Rhythm Disorders in Children and Adults", ANUBIH, 2013.
- International Symposium: "Acquired and Genetically Predisposed Disease of the Heart in Children", ANUBiH, Book 45, 2014.
- International Scientific Symposium: "Foetal Medicine: From Leonardo da Vinci to Date", ANUBIH, Book 46, 2015.
- International Scientific Symposium: "Mitral Valve Diseases in Children and Adults", ANUBiH, Book 49, 2017, English edition.
- Symposium: "Health Management with Special Attention to Cardiovascular Diseases", ANUBiH, Book 52, 2018, English edition.
- International Scientific Symposium: "Heart and…", ANUBiH, Book 54, 2019 English edition

Amid the marking of the World Heart Day, the Board for Cardiovascular Pathology of the Department for Medical Sciences of ANUBiH traditionally organizes:

- **XII and XIII International Scientific Symposium "Diagnostics in cardiology and GUCH"**

The aim of this International Scientific Symposium, held on 15 April 2021, was to evaluate:

- news in cardiovascular diagnostic medicine
- new approach in paediatric cardiosurgery
- diagnostic cardiac catheterisation
- foetal echocardiography
- genetics of cardiomyopathy
- MRI in paediatric cardiology
- diagnostics of rhythm disorders in children and adolescents
- echocardiography
- diagnostics of preventable diseases in cardiology
- grown up congenital heart disease
- current guidelines for cardiac diagnostic workup during COVID-19 infection
- risk factors for development of cardiovascular diseases,
- diagnostic-therapeutic algorithms of cardiovascular diseases in paediatric and adult population,
- observance and prevention of cardiovascular diseases,
- professional promotion of systemic interventions,
- advancement of healthcare in accordance with the EU guidelines.

Target audience

The intended audience includes practicing cardiologists, adult cardiologists, paediatric cardiologists, cardiovascular surgeons, cardiovascular and internal medicine trainees, emergency medicine, internal medicine, family medicine specialists and trainees, physician assistants, specialists of public health, students, masters, magistrates and PhD doctors of medicine, health faculties, nurse practitioners, nurses, and any staff with a cardiovascular interest.

Participants of this Symposium:

- Prof.dr.sci.med. Daniel Zimpfer, Medical faculty, University Wien; AKH; "Surgical Treatment of Congenital Aortic Valve Disease".
- Prof.dr.sci.med. Hakan Ucar, Medical faculty, University Istanbul: "Diagnostic Cardiac Catheterisation Test"
- Prof.dr.sci.med. Samo Vesel, Medical faculty, University Ljubljana, Slovenia: "Foetal Echocardiography"
- Prof.dr.sci.med. Amina Kozarić, UCU Sarajevo, IUS Sarajevo: "Genetics of Cardiomyopathy"
- Prof.dr.sci.med. Ida Jovanović, Medical faculty University Beograd: "MRI in Paediatric Cardiology"
- Prof.dr.sci.med. Goran Vukomanović, Medical faculty University Beograd: "Diagnostics of Rhythm Disorders in Children and Adolescents"
- Prof.dr.sci.med. Tugcin Bora Polat, Medical faculty, University Istanbul, "Echocardiography"
- Prof.dr.sci.med. Senka Mesihović-Dinarević, Medical faculty University of Mostar: "Update in Diagnostics Cardiology"
- Prof.dr.sci.med. Aida Pilav, Faculty of health studies, University of Sarajevo: "Diagnostics of Preventable Diseases in Cardiology"
- Prof.dr.sci.med. Zumreta Kušljugić, Medical faculty University of Tuzla: "Grown Up Congenital Heart Disease"





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GENETICS OF CARDIOMYOPATHY

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Abstract

Heart failure is a leading cause of morbidity and mortality. Around 4% of patients with heart failure carry a pathogenic genetic aberration that causes cardiomyopathy and subsequently leads to heart failure. There are five types of primary genetic cardiomyopathies that can give rise to heart failure: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, arrhythmogenic cardiomyopathy (ACM), restrictive cardiomyopathy (RCM), and left ventricular noncompaction (LVNC). If genetic cardiomyopathy is suspected, genomic/genetic testing is recommended because it provides the underlying cause for the diagnosis, prognostic parameters, and possibility to test family members at risk. Testing should be conducted as part of a multidisciplinary approach by a team of adult or paediatric cardiologists, geneticists, and genetic counsellors. Here we will discuss 1) different genomic testing approaches and the management of variants of uncertain significance, 2) management of patients with suspected genetic cardiomyopathy in a multidisciplinary team, and 3) the associations between genotypes and phenotypes of most commonly mutated genes such as *MYH7, TNNT2, TPM1, MYBPC3*, *TTN*, and others. In conclusion, genetic testing of patients with cardiomyopathies helps with proper diagnosis, prognosis, treatment, and identification of relatives at risk.

Key words: genetics, cardiomyopathy, hypertrophic cardiomyopathy, next generation sequencing, genetic counseling

Introduction

Cardiomyopathy represents heterogeneous group of diseases of the heart muscle, where the heart walls have changed by being thickened, stretched, or stiff. Subsequently, the heart function is affected. In 2006, the American Heart Association's Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care

and Outcomes of Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention recommended that cardiomyopathies can be most effectively classified as primary and secondary. Primary cardiomyopathies are driven by heart-specific factors (the heart is the primary affected organ), while secondary cardiomyopathies are part of a systemic disorder (the heart is affected along with other organs). Primary cardiomyopathies are further classified into: genetic, mixed (genetic and non-genetic), and acquired [1] (Figure 1). In this review, we will focus on the genetic causes of primary cardiomyopathies.

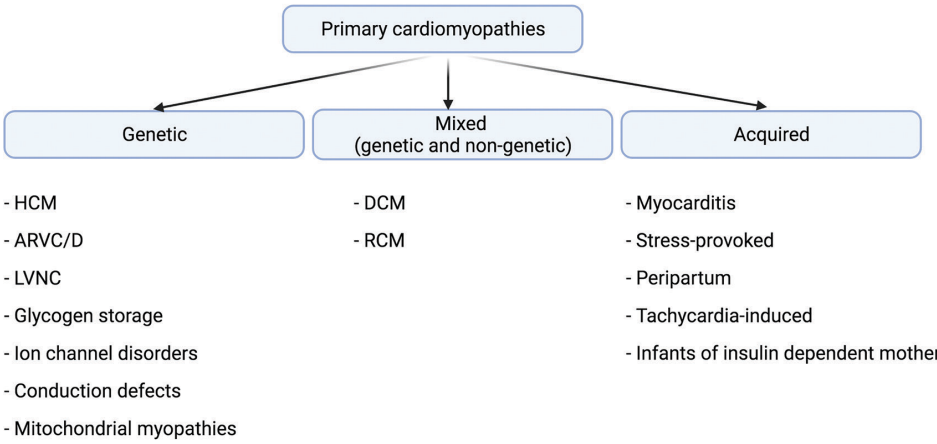

Figure 1. Primary cardiomyopathies are classified into genetic, mixed and acquired. Hypertrophic cardiomyopathy (HCM); arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D); left ventricular noncompaction - LVNC; dilated cardiomyopathy (DCM); restricted cardiomyopathy (RCM). Adapted from [1].

Primary genetic cardiomyopathies are: hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), and left ventricular non-compaction (LVNC), glycogen storage diseases, conduction defects, mitochondrial myopathies, and ion channel disorders (Brugada, LQTS, SQTS, CVPT, and Asian SUNDS) [1,2]. Mixed primary cardiomyopathies that have both genetic and non-genetic components include: dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). Acquired primary cardiomyopathies can be: myocarditis, stress-provoked, peripartum, tachycardia-induced, infants of insulin-dependent diabetic mothers.

Secondary cardiomyopathies of genetic origin are for example Fabry disease (lysosomal storage disease caused by mutations in *GLA* gene), Noonan syndrome (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, and *KRAS* genes), muscular dystrophy (DMD gene and others), Friedrich's ataxia (*FXN* gene), and hemochromatosis (*HFE* gene and others). Secondary cardiomyopathies of acquired causes are diabetes mellitus, hyperthyroidism, hypereosinophilic syndrome, sarcoidosis, etc.

As discussed above, primary cardiomyopathies can be caused by mutations in specific genes. Genes are long segments of DNA, which is situated within the nucleus of each cell in the body. DNA is a double helix consisting of two antiparallel chains made up of four building blocks: adenine, guanine, cytosine and thymine (Figure 2).

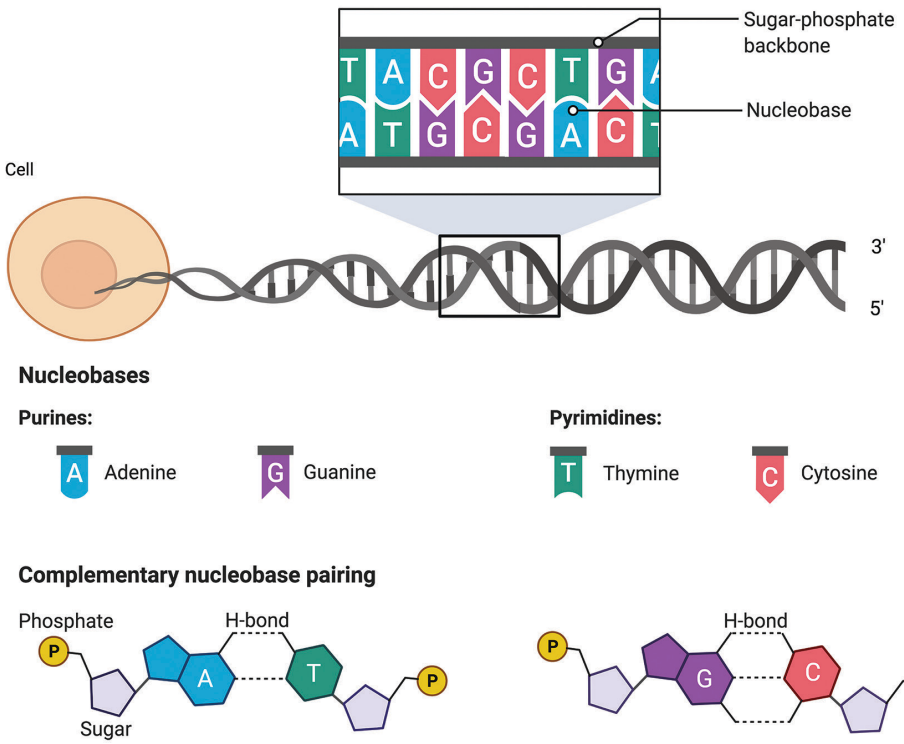

Figure 2. DNA is found in the nucleus of the cell. Building blocks of DNA are four bases: adenine, guanine, thymine, and cytosine, which are connected with a sugar phosphate backbone into a single molecular or chain. DNA has two antiparallel chains in the form of a double helix. Within the DNA helix, adenine pairs with thymine and cytosine pairs with guanine.

The DNA sequence in a gene is used to direct the correct sequence of proteins (the central dogma of biology: DNA-RNA-protein). Genes code for proteins that carry out various functions within the body including building organs or metabolizing various substances. Mistakes in the coded instructions (DNA) are called mutations, which can affect the proper structure and function of proteins (Figure 3). For example, DNA mutations in genes that code for proteins important for the function of heart cells can lead to cardiomyopathies.

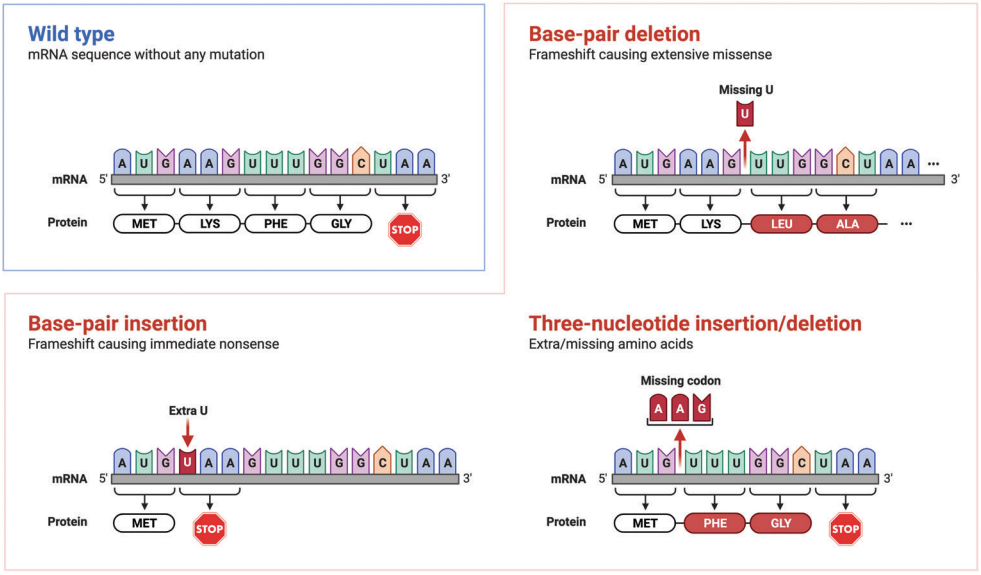

Figure 3. Mutations in DNA (or its copy in the form of RNA) can be single base pair mutations (not shown), duplications, deletions, insertions, or inversions (not shown). Mutation can have different effects on protein function: from no effect to deleterious effect, thus from benign to pathogenic effect.

Defining genomic terms and patterns of inheritance

The era of genomic medicine has impacted the field of cardiology as well, especially understanding the causes of cardiomyopathies. Mutations can be single point mutations, deletions, duplications, inversions, and insertions. Mutations in genes have five designations, depending on the effect on phenotype: pathogenic, likely pathogenic, variant of unknown significance, likely benign, and benign.

If an individual is a carrier of a germline mutation in genes associated with cardiomyopathy, they have a risk of passing the mutation to their offspring. Germline mutations can be inherited in autosomal dominant, autosomal recessive or X-linked manner. For autosomal dominant disorders, the patient has a DNA mutation in one copy of the gene, while the other copy is normal (wild type). Therefore, the offspring of that patient has a 50% chance to inherit the mutation. Autosomal dominant inheritance is defined as a disease where one copy of a mutation is sufficient to cause the disease. In a family with an autosomal dominant condition, offspring have a 50% chance of having the disease. In autosomal recessive disorders, both parents are carriers of a mutation, but they do not have the disease (carrier status, no disease). If their child inherits both copies of the mutated gene, the child will have the disease. If a child has a mutation in one copy of the gene, he is the carrier but does not manifest the disease. Children with autosomal recessive diseases have mutations in both copies of a specific gene, which they have inherited from both of their parents. A child with an autosomal recessive cardiomyopathy inherits a defective gene from each of his carrier parents. If both parents are carriers (have the mutation in one copy of the gene), the risk that other children (or future children) will have the cardiomyopathy is one in four, or 25%. Usually, the only individuals in the extended family at risk are brothers and sisters of the child with the cardiomyopathy.

Hypertrophic cardiomyopathy

HCM is a primary cardiomyopathy of genetic origin with heterogeneous clinical presentation [3]. It is a common disease, with prevalence of 1:500 to 1:200. It is an autosomal dominant disease, meaning that it is transmitted to 50% of patient's children and that it was inherited from one of patient's parents. HCM is also the most common cause of sudden cardiac death in younger people including athletes. Morphologically, the heart is hypertrophic with nondilated LV. There is no other underlying disease that could cause the hypertrophy such as hypertension or aortic valve stenosis. The first diagnosis is typically made by echocardiography or MRI; also, ECG alterations may be detected before hypertrophy. Any LV wall thickness, even when it is within normal limits, can be enough to refer the patient for DNA analysis.

HCM is caused by mutations in 11 genes that primarily encode proteins with function in heart cells, specifically contractile proteins in sarcomere. HCM was first associated with mutations in gene *MYH7* in 1989 [4-7]. About

70% of HCM patients have mutations in *MYH7* (β-myosin heavy chain) and *MYBPC3* (myosin-binding protein C). Other HCM genes include: *ACTC1*, *MYL2, MYL3, TNNT2, TNNI3, TPM1, CSRP3, JPH2,* and *TNNC1* (Table 1). There are no hot spot mutations and they are dispersed throughout the mentioned genes. So far, there are more than 1500 mutations identified.

Table 1. Genes involved in hypertrophic cardiomyopathy.

Gene Symbol	Encoded protein	Cellular Location
MYBPC3	Cardiac myosin binding protein C	Sarcomere, thick filament
MYH7	β-myosin heavy chain	Sarcomere, thick filament
MYL2	Regulatory myosin light chain	Sarcomere, thick filament
MYL3	Essential myosin light chain	Sarcomere, thick filament
TNNI3	Cardiac troponin I	Sarcomere, thin filament
TNNT2	Cardiac troponin T	Sarcomere, thin filament
TPM1	α-tropomyosin	Sarcomere, thin filament
ACTC1	Cardiac α-actin	Sarcomere, thin filament
CSRP3	Cardiac LIM protein	Sarcomere, Z line
JPH2	Junctophilin 2	Sarcomere, reticulum membrane
TNNC1	Troponin C1	Actin filament

The genetic cause for a majority of HCM is well established. However, the biochemical and functional mechanisms of how mutations affect sarcomere function disease remain less understood. Physiological mechanisms were better understood when HCM mutations were introduced into mice; for example, mutations in the myosin head region show enhancement of contraction, but inability for relaxation (myosin head region is the domain that generates force, hydrolyses ATP, and interacts with other sarcommeric proteins).

Genotype-phenotype relationship, or how specific mutation affects the clinical presentation and severity of disease, is not straightforward in HCM. Large families with specific HCM mutations have provided an insight into how genotype can affect phenotype. For example, it is known that poor clinical outcome is associated with several *MYH7* mutations: Arg403Gln, Arg719Trp, and Arg453Cys. Arg403Gln is associated with increased risk for sudden cardiac death, while Arg719Trp and Arg453Cys are associated with heart failure [8-10]. However, other mutations in *MYH7* have milder phenotype. Mutations in *MYBPC3* are associated with later onset and milder phenotype.

HCM can be found in other diseases such as Fabry (*GLA* gene), amyloidosis (*TTR* gene), Noonan syndrome (*PTPN11*, *SOS1*, *RAF1*, *RIT1*, and *KRAS* genes), glycogen storage disease (*PRKAG2*), Danon (*LAMP2*), and others. These diseases can have clinical presentation only in the heart and can mimic HCM. Thus, these genes should be considered for testing in appropriate clinical presentation. *PRKAG2* gene encodes the gamma-2-regulatory subunit of the AMP-activated protein kinase (*PRKAG2*) and is associated with variable degrees of LV hypertrophy and ventricular pre-excitation [11]. *LAMP2* is lysosome associated membrane protein 2 resulting in Danon-type storage disease [1]. Clinical manifestations are confined to the heart abnormalities, presenting with massive degrees of LV hypertrophy and ventricular pre-excitation. These disorders are now part of a subgroup of previously described infiltrative forms of LV hypertrophy such as Pompe disease and Fabry's disease, an X-linked recessive disorder of glycosphingolipid metabolism caused by a deficiency of alpha-galactosidase A [8]. Several other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring in infants and children less than 4 years of age, may resemble HCM caused by sarcomere mutations. These cardiomyopathies include Noonan syndrome, an autosomal dominant cardiofacial condition associated with a variety of cardiac defects.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)

ARVC/D is a rare form of heart disease (1:5000) that was first described about 20 years ago. It is regarded as a common cause of sudden death in athletes, diagnosed typically in third to fifth decade of life. It involves primarily the right ventricle with progressive loss of myocytes that are replaced by fibrofatty tissues. Clinical presentation usually involves ventricular tachyarrhythmias. ARCV/D can be transmitted in autosomal dominant or recessive manner, depending on the involved gene. In most cases, it is autosomal dominant inheritance but with incomplete penetrance. Four genes are primarily associated with ARCV/D: *RYR2, DSP, PKP2*, and *TGFB3*. Other genes associated with ARVC/D are: *ANK2, CTNNA3, DES, DSC2, DSG2, JUP, LMNA, SCN5A, TMEM43*, and *TTN* (Table 2). Plakophilin-2, *PKP2*, (ARVC9) gene mutations can be found in more than one third of ARVC patients [12, 13].

Table 2. Genes involved in Arrhythmogenic right ventricular cardiomyopathy/dysplasia.

Gene	Encoded Protein	Localization
RYR2	Ryanodine receptor 2	Sarcoplasmic reticulum
DSP	Desmoplakin	Carvajal syndrome
PKP2	Plakophilin 2	Nucleus, desmosome
TGFB3	Transforming Growth Factor Beta 3	extracellular matrix

JUP (Naxos syndrome), *DSP* (Carvajal syndrome), and *DSC* are inherited in autosomal recessive manner, and cause pulmoplanar keratoderma and woolly hair. Desmoplakin, *DSP* gene, was first identified and associated with ARVD (ARVD8) which causes Carvajal syndrome. The protein product of *DSP* gene is the key component of desmosomes and adherens junctions which are important for maintaining the tight adhesion. Once the junctions are disrupted, cell death and fibrofatty replacement take place [14]. Similarly to Carvajal syndrome, ARVD/C can also be associated with Naxos syndrome, an autosomal recessive disorder caused by mutations in the plakoglobin protein (*JUP* gene) with similar phenotypic presentation to Carvajal syndrome [15,16]. Like desmoplakin, plakoglobin is a key component of desmosomes and participates in maintaining tight cell-cell adhesion.

Left ventricular Noncompaction - LVNC

Left ventricular noncompaction is a recently discovered congenital cardiomyopathy with a characteristic morphological appearance of LV. It has prevalence of 0.05% to 0.3%. It often coexists with other cardiomyopathies. Three genes associated with LVNC are: *TAZ*, *MIB1*, and *MYH7*. Besides them, other genes are also associated with LVNC: *ACTC1, LDB3, LMNA, MYBPC3, TNNT2,* and *TPM1* (Table 3). TAZ (also known as *TAFAZZIN* or G4.5) is a gene that encodes a mitochondrial transacylase that catalyses remodelling of immature cardiolipin to its mature composition containing a predominance of tetralinoleoyl moieties. It is an X-linked condition and causes Barth syndrome.

Table 3. Genes involved in Left ventricular Noncompaction – LVNC

Gene	Encoded Protein	Associated findings or syndromes*
TAZ	Tafazzin	DCM, Barth syndrome
MIB1	Mindbomb homolog 1	None
MYH7	Myosin heavy chain	None

Metabolic disorders associated with primary cardiomyopathy

Glycogen storage diseases (GSD) are metabolic disorders caused by enzyme deficiencies affecting glycogen synthesis, glycogen breakdown, or glycolysis. There are at least 15 types of GSD, where two types are associated with primary HCM, namely Pompe disease caused by *GAA* mutations and *PRKAG2* syndrome (Table 4). *Pompe disease* (three forms: infantile, juvenile and adult-onset) is an autosomal recessive disorder that results from the deficiency in the enzyme acid alpha-glucosidase (GAA), causing the abnormal glycogen accumulation in all tissues [17]. *PRKAG2 syndrome* is a rare, early-onset autosomal dominant inherited disease, characterized by ventricular pre-excitation, supraventricular arrhythmias and cardiac hypertrophy. *PRKAG2* mutations are characterized by glycogen accumulation in the cardiac tissue.

Table 4. Genes involved in Metabolic disorders associated with primary cardiomyopathy

Gene	Encoded Protein	Disease	Inheritance
GLA	α-galactosidase A	Fabry disease	*X*-linked
LAMP2	Lysosome-associated membrane protein 2	Danon disease	*X*-linked
PRKAG2	AMP-activated protein kinase, g2 subunit (noncatalytic)	PRKAG2 cardiomyopathy	Autosomal dominant
GAA	α-glucosidase	Pompe disease	Autosomal recessive

Lysosomal storage disease associated with primary cardiomyopathy is *Danon syndrome* caused by lysosome associated membrane protein 2 (LAMP2) [18]. Clinical manifestations are confined to the heart abnormalities, presenting with massive degrees of LV hypertrophy and ventricular pre-excitation, as well as neurocognitive deficits and hepatic dysfunction with very poor prognosis and early triage to heart transplantation. It is an autosomal dominant disease.

GLA mutations cause Fabry disease with left ventricular hypertrophy as well as renal, eye, and skin manifestations [18]. Recognition of Fabry cardiomyopathy has critical therapeutic implications, because early treatment such as enzyme replacement therapy can be beneficial because it limits myocardial remodelling and maintains cardiac function [19-21].

Ion channelopathies

In the last several years, there has been a growing understanding of the rare congenital arrhythmia disorders that include LQTS (long QT syndrome),

SQTS (short-QT syndrome) Brugada syndrome, CPVT (catecholaminergic polymorphic ventricular tachycardia) and idiopathic ventricular fibrillation, that are all caused by mutations in ion channel genes responsible for defective functioning of sodium and potassium channels [1].

The most common ion channelopathy is LQTS, which can be inherited in autosomal recessive and autosomal dominant manner. Autosomal recessive forms are associated with deafness and are caused by mutations in *KCNQ1* gene (Jervell syndrome) and *KCNE1* gene (Lange-Nielsen syndrome). Autosomal dominant LQTS is caused by mutations in 8 genes: *SCN5A* (Na1.5, LQT3), *KCNQ1* (KvLQT1, LQT1), *ANKB* (LQT4), *KCNE1* (minK, LQT5), *KCNE2* (MiRP1, LQT6), *KCNH2* (HERG, LQT2) *KCNJ2* (Kir2.1, LQT7, Andersen's syndrome), and *CACNA1C* (Ca1.2, LQT8, Timothy syndrome) (Table 5).

Table 5. Genes involved in Brugada syndrome.

Gene name	Function
SCN5A	NaV1.5 – α subunit of the cardiac sodium channel carrying the sodium current
GPD1L	Glycerol-3-phosphate dehydrogenase like peptide
CACNA1C	CaV1.2 – α subunit of voltage-dependent calcium channel
CACNB2	CaVβ2B – β-2 subunit of the voltage-gated calcium channel
SCN1B	NaVβ1 – β-1 subunit of the sodium channel
KCNE3	MiRP2 – β subunit to voltage-gated potassium channels
SCN3B	NaVβ3 – β-3 subunit of the cardiac sodium channel
HCN4	Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 4
KCND3	KV4.3, α-subunit of the transient outward potassium channel
CACNA2D1	α2δ subunit of the voltage-gated calcium channel
RANGRF	MOG1
ABCC9	SUR2A, the adenosine triphosphate (ATP)-binding cassette transporter of the IK(ATP) channel
SCN2B	NaVβ2 – Beta-2 subunit of the cardiac sodium channel
SCN10A	NaV1.8 – α subunit of the neuronal sodium channel

Brugada syndrome was first described in 1992 and is characterized by distinct ECG pattern and increased risk of sudden cardiac death, especially SUDS [22-24]. It is an autosomal dominant disease, where the most common mutation is in *SCN5A* gene (20% of patients with Brugada syndrome, also called Brugada syndrome type 1). OMIM recognizes 9 types of Brugada syndrome. Type 2 is caused by mutation in *GPD1L*, type 3 by mutations in

CACNA1C, type 4 by mutations in CACNB2, type 5 *SCN1B*, type 6 by mutations in *KCNE3*, type 7 by mutations in *SCN3B* gene, type 8 by mutation in the *HCN4*, and type 9 by mutations in *KCND3*.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a primary cardiomyopathy of mixed origin, with both genetic and non-genetic (acquired) causes [25]. About 35% of DCM is genetic. Non-genetic causes include infectious, autoimmune, toxic, peripartum, drug-induced, and others. In DCM, wall thickness is normal, while left ventricular mass is increased due to enlarged myocytes, myocardial fibrosis that promotes arrhythmias and heart failure. Prevalence is about 1:250. Patients with DCM are the most frequent candidates for heart transplant [26]. DCM may be more difficult to diagnose genetically because clinical presentation may overlap with other cardiovascular diseases and some patients develop it late in life. Also, some gene panels are quite limiting, and may lead to missed DCM diagnoses.

More than 50 genes are involved in pathology of DCM with function in cytoskeleton, sarcomere, sarcolemma, etc. Most genes are involved in autosomal dominant inheritance. Mutations affecting sarcomere, such as *MYH7, TNNT2, TPM1, MYBPC3* and *TTN* are commonly mutated in DCM, where *TTN* accounts for up to 25% of all DCM mutations.

Table 6. Genes involved in dilated cardiomyopathy.

Gene	Protein	Percent mutated in DCM	Localization and coexistent phenotypes
TTN	Titin	15%-25%	None
MYH7	β-myosin heavy chain	10%	None
MYH6	α-myosin heavy chain	6%	Sarcomere
MYPN	Myopalladin	3%-4%	Sarcomere, Z disc
DSP	Desmoplakin	3%-4%	Desmosome
ACTC1	Cardiac α-actin	<1%	None
TNNT2	Cardiac troponin T	3%	None
TPM1	α-tropomyosin	<1%	None
TNNI3	Cardiac troponin I	<1%	None
BAG3	Bcl2-associated athanogene 3	<1%	None
DES	Desmin	<1%	Skeletal myopathy, conduction system disease

Gene	Protein	Percent mutated in DCM	Localization and coexistent phenotypes
DMD	Dystrophin	<1%	Duchenne's muscular dystrophy, Becker's muscular dystrophy
DNAJC19	DNAJ (Hsp40) homolog	<1%	DCMA
EMD	Emerin	<1%	Emery-Dreifuss muscular dystrophy type 1
LMNA	Lamin A/C	6%	Conduction system disease, Emery-Dreifuss muscular dystrophy type 2
PLN	Phospholamban	<1%	None
RBM20	RNA-binding protein, 20	5%	None
SCN5A	Voltage gated sodium channel type V, α-subunit	3%	Supraventricular and ventricular arrhythmias
TAZ	Tafazzin	<1%	Barth syndrome

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is the rarest form of primary cardiomyopathy, accounting for ~5% of primary cardiomyopathies [26]. It can be caused by genetic or non-genetic causes. Genes involved include troponin T (*TNNT2*), troponin I (*TNNI2*), α-actin (*ACTC1*), β-myosin heavy chain (*MYH7*), and filamin C (*FLNC*).

Patient management

Genetic testing and counselling are highly recommended for patients with suspected primary cardiomyopathy. Genetic counselling should be coordinated with a multidisciplinary team of cardiologists, genetic counsellors, and laboratory geneticists. The choice of a proper genetic test is important and should be discussed with the genetic counsellor and laboratory geneticist. There are 3 major test types: gene panel, WES (whole exome sequencing), and WGS (whole genome sequencing). Gene panels are tests that include sequencing of exons of many genes (up to ~100, depending on the company). Gene panels can be specific for a particular type of primary cardiomyopathy, such as HCM, DCM, etc. WES is a test that includes all genes, ~25000. WES is more expensive but gives more information and can be used to find mutations in rare genes, increasing the sensitivity of the test. On the contrary, besides cardiomyopathy-related findings, patient should be counselled that other genes might be picked up that carry mutations unrelated to the original indication.

Variants of unknown significance (VUS) may also be found, which can add additional complexity to the treatment algorithm. WGS is a comprehensive and expensive method to test all DNA, including genes, and other types of DNA including mitochondrial DNA, this being able to pick up rare intronic variants in cardiomyopathy-related genes. Often, WES and WGS are used for research purposes only and not in standard diagnostic setting; however, depending on the cost and insurance, clinicians may be more likely to order WES. ACC/AHA recommends using gene panel testing for HCM [3].

Regarding the interpretation of variants, ACMG (American College of Medical Genetics and Genomics) should be consulted, as well as ClinVar. If a patient carries a VUS, they should be re-evaluated every couple of years and ClinVar checked to see if the classification status has changed.

Testing of the proband, as it is the case in other genetic diseases, involves the family too. If the patient is a carrier of a pathogenic variant, their at-risk relatives should be informed as well.

Genotype-phenotype correlations are still largely unknown and may not be a part of routine genetic counselling session for primary cardiomyopathies. It is important to note that in primary cardiomyopathies, the same gene mutation (genotype) can have different phenotypes (DCM, HCM, RCM and ACM). For example, *MYH7* mutations can cause HCM, DCM, RCM or LVNC. Gene identification can also help with finding possible 'mimics' such as Fabry disease, glycogen storage disease, or others. Also, it can help with early start of proper therapy. Gene mutations can also identify patients with early onset of left ventricular arrhythmias. For example, *LMNA* mutation carriers have a higher risk of conduction disease, atrial and ventricular arrhythmias. DCM-associated genes *PLN, FLNC, TMEM43*, and DES have higher risk of ventricular arrhythmias, as well as *TTN* [27].

Similar to adults, families with a child diagnosed with cardiomyopathy are at an increased risk for another at-risk child or family member. When a pathogenic variant is diagnosed within the family, all of the family members (brothers, sisters, and parents) should be screened with an echocardiogram. Depending on the type of cardiomyopathy diagnosed, it may be necessary to repeat the echocardiogram periodically for younger children (childhood to mid-adult life). In infants, cardiomyopathies can be caused by inborn errors of metabolism that are inherited in an autosomal recessive fashion as discussed previously. Duchenne or Becker muscular dystrophy or Barth syndrome are

examples of X-linked inherited diseases that are found in males only, while females are carriers.

Primary cardiomyopathies are generally caused by genetic mutations leading to the development of HCM, DCM, RCM, LVNC and ARVC. Genetic testing is important for proper diagnosis, treatment as well as patient prognosis. Testing of at-risk relatives can identify those who will develop cardiomyopathy, helping to start early treatment.

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GENETIKA KARDIOMIOPATIJE

Apstrakt

Zatajenje srca vodeći je uzrok morbiditeta i mortaliteta. Oko 4% pacijenata sa zatajenjem srca nosi patogenu genetsku aberaciju koja uzrokuje kardiomiopatiju, što posljedično dovodi do zatajenja srca. Postoji pet vrsta primarnih genetskih kardiomiopatija koje mogu uzrokovati zatajenje srca: hipertrofična kardiomiopatija (HCM), dilatativna kardiomiopatija, aritmogena kardiomiopatija (ACM), restriktivna kardiomiopatija (RCM) i nekompakcija lijeve komore (LVNC). Ako se sumnja na genetsku kardiomiopatiju, preporučuje se genomsko/genetsko testiranje, jer pruža temeljni uzrok za dijagnozu, prognostičke parametre i mogućnost testiranja rizičnih članova porodice. Testiranje bi trebalo biti provedeno kao dio multidisciplinarnog pristupa od strane tima kardiologa za odrasle ili za djecu, genetičara i genetskih savjetnika. U ovome radu ćemo raspravljati o: 1) različitim pristupima genomskom testiranju i upravljanju varijantama neizvjesnog značaja; 2) liječenju pacijenata sa sumnjom na genetsku kardiomiopatiju uz pomoć multidisciplinarnog tima; i 3) povezanosti između genotipova i fenotipova najčešće mutiranih gena poput *MYH7*, *TNNT2*, *TPM1*, *MYBPC3*, *TTN* i drugih. Zaključujemo da genetsko testiranje pacijenata s kardiomiopatijama pomaže u pravilnoj dijagnozi, prognozi, liječenju i identifikaciji ugrožene rodbine.

Ključne riječi: genetika, kardiomiopatija, hipertrofična kardiomiopatija, sekvenciranje sljedeće generacije, genetsko savjetovanje

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Update in diagnostics cardiology
Review article

UPDATE IN DIAGNOSTICS CARDIOLOGY

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Abstract

Cardiovascular medicine is an area of clinical practice with a continually rapid expansion of knowledge, guidelines, best practices and new technology in adult cardiovascular medicine as well as in paediatric cardiology medicine. Cardiovascular diseases (CVD) are the leading cause of mortality in the world and cause major costs for the health sector and economy. Cardiovascular imaging indices have a significant impact on the prevention, diagnosis, and treatment of cardiac diseases. Advanced imaging technologies have dramatically improved our ability to detect and treat cardiovascular disease at an early stage. Multimodality imaging techniques - echocardiogram, cardiac computerized tomography, magnetic resonance imaging, simulation 3D models, artificial intelligence - are being used more frequently as their utility is better appreciated.

Coronavirus disease 2019 (COVID-19) exerts an unprecedented global impact on public health and health care delivery. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 has reached pandemic levels since March 2020. Patients with cardiovascular (CV) risk factors and established CVD represent a vulnerable population when suffering from COVID-19, and have an increased risk of morbidity and mortality. Severe COVID-19 infection is associated with myocardial damage and cardiac arrhythmia. Diagnostic workup during SARS infection revealed electrocardiographic changes, sub-clinical left ventricular (LV) diastolic impairment and troponin elevation.

All professionals in cardiovascular medicine, as a part of lifelong learning process, have the continuous imperative in reviewing novelties, with results data from numerous researches in order to treat all patients according to best practices and evidence-based medicine, especially on this journey through corona pandemic.

Key words: diagnostics, cardiology, up to date

Cardiovascular medicine is an area of clinical practice with a continually rapid expansion of knowledge, guidelines, best practices and new technology in adult cardiovascular medicine as well as in paediatric cardiology medicine (1). Cardiovascular diseases (CVD) are the leading cause of mortality in the world and cause major costs for the health sector and economy. Although during the last two decades rates of cardiovascular mortality declined in many developed countries, they have grown in low- and middle-income countries. Primary care clinicians are challenged to optimally manage a multitude of diseases involving the cardiovascular system, including the heart failure, arrhythmias and the circulation affected by abnormal cholesterol metabolism and hypertension. The majority of CVDs can be prevented by addressing behavioural risk factors such as tobacco use, unhealthy diets and obesity, physical inactivity and harmful use of alcohol, using a population wide strategy (2). *Innovative technologies* in the world of cardiovascular medicine are expanding every day such as: wearable computing technologies, bioresorbable stents, leadless pacemaker, valve-in-valve procedure, protein patch for heart muscle growth and others (3).

In the section of *Adult Cardiology,* we are going *to review* a few novelties which would be of interest *for primary care practitioners*.

Artificial intelligence (AI) is defined as the ability of computer systems to perform tasks humans usually perform. Machine learning, while often used interchangeably with AI, is actually a subset of AI in which algorithms, mathematical models and/or computer systems are used to optimize the performance of a given task (4). The *Six broad* areas in which AI will advance the cardiovascular field are: *1. Novel drug discovery/development*. AI is increasingly being used to refine the selection of potential therapies by searching for patterns in molecular biology, structure-function, and clinical trial databases; *2. Precision medicine.* With AI, genetic information, environment and lifestyle can be quickly assessed to determine who is most likely to benefit from certain interventions; *3. Integration of data from varied sources*. AI enables data from varied sources, such as wearables, social media, the electronic health record, to be integrated into models that can predict the trajectory of both health and disease; *4. Improved efficiency.* AI can help reduce provider dissatisfaction and burnout by minimizing repetitive tasks, prioritizing HER (Health Electronic Record) - based alerts or messages, improving and automating image interpretation in the catheterization or echocardiography laboratory, and presenting a “preferred” treatment plan based on integration

of varied data sources; *5. Remote monitoring.* AI can strain out clinically actionable data from the trillions of data bytes wearable devices collect; *6. Increasing the value of delivered care*. Artificial intelligence is an ideal population tool, given its ability to better predict individuals at greater or lesser risk of developing chronic diseases or related complications, tailoring preventive therapies and allocating limited resources to those most likely to benefit from them. No emerging technology has more promise than AI. There are dozens of articles about the potential for AI in health care and an increasing number of scientific publications. But, overall, almost nothing has yet made its way into clinical practice. One likely reason is that many start-up and established tech companies underestimated the complexity of health care data and the need to provide strong evidence that the use of AI would improve efficiency and outcomes. It's therefore important that clinicians insist on strong data before relying on AI.

Another aspect of novelty in cardiovascular diagnostics medicine that has been discussed is *Patient-Generated Data:* The first "wearable" in cardiovascular medicine dates back to the 1800s, when a watch with a second hand was used to measure heart rate (4). Today, however, wearables are more likely to be patient initiated, measuring everything from heart rate and rhythm to blood pressure, sleep quality and duration, and physical activity (5,6). There is particular interest in the ability of wearables to affect clinical outcomes in cardiovascular disease. A major trial evaluating the potential of specialized software for the Apple Watch to detect abnormal heart rhythms is underway. The Apple Heart Study, a virtual, prospective, single-arm pragmatic study has enrolled more than 400.000 participants. The primary outcome is the proportion of participants with an irregular pulse detected by the watch who are diagnosed with AF on subsequent ambulatory ECG patch monitoring. A secondary outcome is to estimate the rate of initial contact with a healthcare provider within three months after the patient is notified of a pulse irregularity (8). To date, data on clinical outcomes from mHealth devices are primarily based on case studies. For instance, Martin and his colleagues recently reported on the case of a woman with paroxysmal AFib whose Apple Watch/Cardia Band detected tachycardiomyopathy, enabling early identification and treatment and likely preventing significant morbidity (7,8,9). This represents the beginnings of mHealth being integrated into clinical care.

Acute myocarditis has been evaluated in the section of *cardiovascular imaging techniques*, discussing several points: the challenge to diagnose

acute myocarditis given its varied clinical manifestations. *Cardiovascular magnetic resonance (CMR)* is a key noninvasive test for acute myocarditis as it enables identification of the location and extent of myocardial involvement, but the optimum CMR protocol for identification of acute myocarditis has not been established. A systematic review and meta-analysis included 22 studies comparing the diagnostic accuracy of CMR techniques for acute myocarditis (10). These findings will help refine CMR protocols for the diagnosis of acute myocarditis. Limited data are available on the agreement between left ventricular ejection fraction (LVEF) measurements by various cardiac imaging modalities. The largest available study of *intermodality variability of LVEF* analysed core lab data from an international trial enrolling patients with coronary artery disease and reduced LVEF including *echocardiograms, single-photon emission computed tomography, and cardiac magnetic resonance (CMR) imaging* (11). Correlation between LVEF determined by quantitative versus visual echocardiographic methods was greater than the correlation between LVEF assessed by different modalities (such as biplane echocardiography versus CMR). In paired comparisons of LVEF by differing imaging modalities, approximately half fell within a range of five absolute percentage points. These observations demonstrate a significant limitation of using LVEF thresholds to guide clinical management and suggest that serial follow-up of a given patient may be best accomplished using a consistent imaging modality. Most published studies suggest that *coronary computed tomography angiography (CCTA) and stress testing (with stress imaging)* are associated with comparable long-term clinical outcomes in stable patients with suspected coronary artery disease (CAD) and in patients with acute chest pain. In the SCOT-HEART trial, which compared standard care (contemporary medical therapy and diagnostic testing at the discretion of the treating physician) with standard care plus CCTA in over 4100 patients with stable chest pain, patients randomized to CCTA with standard care had a reduction in the primary endpoint of CAD death or non-fatal myocardial infarction (2.3 versus 3.9 percent) over an average follow-up of 4.8 years (12). In contrast to prior studies comparing CCTA with stress testing, however, 85% of patients underwent stress electrocardiography (ECG) alone, with only 9 percent subsequently undergoing a stress test with imaging. Ongoing studies of CCTA should provide additional guidance regarding its optimal role in the diagnosis of patients with chest pain and suspected CAD.

Hypertension is one of the risk factors for development of cardiovascular diseases. Numerous epidemiological studies have found an association between incrementally higher blood pressure in middle-aged and older adults and the risk of cardiovascular disease in middle-aged and older adults; fewer data are available for the outcomes of *high blood pressure among young adults.* Two large prospective cohort studies of adults younger than 40 years at baseline found that increments in blood pressures >120/>80 mmHg, compared with a blood pressure <120/<80 mmHg, were associated with increasing risk for coronary heart disease and stroke later in life (13,14). These studies support that hypertension, defined by the 2017 ACC/AHA guidelines as blood pressure ≥130/≥80 mmHg, is an important risk factor for cardiovascular disease, including in young adults. The American Heart Association updated their statement on detection, evaluation, and management of *resistant hypertension* (uncontrolled hypertension despite prescription of three or more antihypertensive medications) (14). The most notable change from prior guidelines relates to the diagnosis of true resistant hypertension. True resistance must be distinguished from pseudo resistance by confirming that blood pressure is above goal when measured in the office using proper technique, by then confirming uncontrolled hypertension with out-of-office measurements (i.e., ambulatory blood pressure monitoring or home blood pressure monitoring), and by considering and excluding nonadherence to antihypertensive therapy.

In the current era, *multimodality imaging techniques* are being used more frequently as their utility is better appreciated (15). Echocardiography has been the mainstay approach, cardiac computerized tomography and magnetic resonance imaging provide a good imaging alternative for patients with multiple complex surgeries. 3D printing has seen a rapid growth in use for planning treatments for patients with congenital heart disease. Simulation using 3D models is emerging as a fundamental resource for teaching procedural techniques and a new standard of care.

Cardiac imaging has a significant influence on the science and practice of paediatric cardiology. Cardiac imaging changed the face of paediatric cardiology. The improvements in the diagnostic modalities of congenital heart disease, especially imaging techniques, surgical and interventional approaches as well as postoperative intensive cardiac therapy and care, have contributed to the significant reduction of prenatal morbidity which is one of the major indicators of the state and level of development of a country. Cardiac

catheterization was the first technique which allowed imaging of the heart and extracardiac vessels by angiography. The development and improvements made in non-invasive imaging techniques, like echocardiography and cardiac magnetic resonance imaging (MRI), have been extremely important. Technical advancements in the field of medical imaging are quickly being made. Techniques such as intracardiac echocardiography, 3D echocardiography, and tissue Doppler imaging are relatively new echocardiographic techniques, which further optimize the anatomical and functional aspects of congenital heart disease. As more information is gathered using these techniques, and is correlated with clinical, hemodynamic and angiographic findings, non-invasive cardiologists have gained greater confidence in understanding images that are viewed. These imagining techniques give a rare satisfaction to those who master them and understand them, resulting in the timely diagnosis and adequate selection of the treatment of congenital heart anomalies.

Cardiac Magnetic Resonance Imaging (MRI) is rapidly developing and is currently becoming increasingly accepted as an important imaging tool in paediatric cardiology. The indications are situated in areas where echocardiography cannot answer clinical questions. A first common indication for the use of cardiac MRI is for better visualisation of extracardiac anatomic structures including the pulmonary arteries with the distal branches, the aorta, the pulmonary veins, and the systemic veins. If there is any doubt about these structures which can be difficult/impossible to visualize using echocardiography because of the interposition of the lungs, MRI is a good alternative to cardiac catheterisation with a high spatial resolution. *Important challenges:* Imaging techniques are changing very quickly and this represents a real challenge for the users of this technology. Training and, afterwards, maintaining competence have become a real challenge. In order to guide training in cardiac imaging, the Association for European Paediatric Cardiology published training guidelines for paediatric echocardiography and cardiac MRI (16,17). Developing competence in paediatric echocardiography is a complex process. A solid foundation is essential to build core knowledge that evolves throughout fellowship, with equal emphasis on both procedural and interpretive skills. Hands-on training through an echo boot camp allows fellows to build a foundation for their procedural skills. An online learning platform develops interpretative skills, it can be accessed by multiple learners irrespective of their location, and is easy to implement once developed and can be user adaptive. The goals of paediatric cardiology training include the acquisition of

cognitive and procedural expertise needed to provide high-quality care to the fetus, infant, and child with congenital and acquired cardiovascular disease and the adult with congenital heart disease, along with the acquisition of the academic skills to make meaningful scholarly contributions to the specialty and to develop the capacity for career-long self-education beyond the years of formal training. No doubt the use of complex tools to refine our diagnostic accuracy will lead us toward the delivery of more sophisticated or patient-specific prevention strategies or therapies. An important consideration for today's imaging innovations is whether a new technique can offer substantial improvements in outcome, safety, or cost. 3D printing has seen a rapid growth in use for planning treatments for patients with congenital heart disease and carries hope in improving quality, efficiency and outcomes of these procedures. The current paradigm of the practice is to identify patients with complex anatomy who may require repeated procedures that carry significant risk. Life-size models by 3D printing using different materials can be used by the surgeon who can then immediately contemplate the approach and the technical feasibility of the anticipated procedure. The use of 3D-printed models can be used to tailor education to different learners, to effectively teach complex cardiac anatomy to radiology, cardiology and cardiovascular surgery fellows. Simulation using 3D models is emerging as a fundamental resource for teaching procedural techniques for trainees acquiring advanced skill sets in the field and is similarly being used within practice as a new standard of care. 3D-printed models are also effective *tools for communication* within health care teams and with patients. Within the practice, specific 3D models used to explain disease processes and planned procedures enhance patient understanding and facilitate shared decision-making and informed consent, which ultimately improves patient satisfaction (18).

The *advances in imaging techniques* (CT, MRI, and echocardiography) that include 3-dimensional imaging and the ability to print models and evaluate anatomy in a virtual environment allow a more thorough preparation for a complex intervention. In addition, the ability to practice the actual procedure in advance of the operation provides an effective model for education and may help reduce morbidity and mortality for complex or infrequently performed percutaneous or open surgical procedures. Imaging and diagnostic capabilities have revolutionized the capacity to care for patients with CHD of all ages. Increasingly the diagnosis of CHD is made during gestation. With increased resolution in imaging, identification of certain features, such as a

restrictive or intact atrial septum in hypoplastic left heart syndrome, can be anticipated and intervened on soon after delivery at centres with expertise in this area, improving outcomes. Advances in imaging and systematic study of quantified parameters, such as indexed right ventricular volumes on magnetic resonance imaging, have helped define thresholds for surgical intervention and improved outcomes. Development of diagnostic parameters such as liver stiffness has assisted the ability to evaluate patients for sequelae of CHD. Additionally, 3D modelling now aids in preoperative planning for patients with complex lesions. This modelling can be particularly helpful *in adult patients with CHD* who have had multiple previous repairs, not infrequently involving surgical techniques that are now extinct. Virtual reality opens another world of possibility in both preoperative planning and education. The complex 3D structure of congenital heart defects can be more completely understood by walking through them and examining every angle. Diagnostic capabilities will also improve with increasing use of molecular and genetic markers, allowing earlier detection and earlier intervention when appropriate. Such advances will make possible personalized treatment based on the molecular fingerprint of the patient›s disease process.

Devices and technology: Current state-of-the-art care of CHD includes a close collaboration between surgeons and interventional cardiologists, with transcatheter interventions assisting before and after surgical interventions, as well as being performed with surgery in hybrid procedures (19). Advances in devices and technology for transcatheter approaches now allow ductal stents as opposed to surgical shunts, percutaneous closure of certain atrial septal defects and percutaneous valve replacements in select patients. Refinement of cardiopulmonary bypass machines, including alterations in oxygenators, safety alarms, and tubing and priming to minimize systemic response to bypass, have improved outcomes. Ventricular assist devices have progressed to become smaller and optimize long-term support, and they are now available for children and even infants. Technological innovations have also led to minimal access surgery and robot-assisted surgery that can be applied in certain teenagers and adults with CHD. Now more than ever a multidisciplinary approach is needed for the care of patients with CHD, with a team of specialists determining the best combination of treatment strategies. On the horizon are further advances in the areas of devices and technology. A subset of CHD progresses during gestation, worsening the severity of the condition and the prognosis for the baby after birth. Fetal cardiac intervention, however,

gives the opportunity to stop or slow such progression, thereby improving the patient's overall prognosis. With technological advancements and refinement of interventional techniques such as ex utero intrapartum treatment, a subset of patients with hypoplastic left heart syndrome have undergone fetal cardiac interventions with evidence of improvement compared with similar patients without intervention. Other congenital cardiac anomalies have the potential of benefiting from fetal cardiac intervention with further study and experience in this burgeoning realm. Other technology and device developments are on the horizon with the potential to significantly improve the ability to care for patients: refinement in transcatheter technology will enable smaller delivery systems-particularly important in small patients with CHD; biomaterials development will lead to implanted materials with fewer issues related to clotting and scarring, with the potential for drug elution technology for specific diseases; tissue engineering is also on the horizon, including biodegradable scaffolds and materials with the potential to grow with the patient; robot-assisted technology will continue to evolve, allowing the potential for use in smaller patients and even in remote surgeries; continued development in assist devices will create implantable devices (as opposed to extracorporeal devices) and smaller devices for the unique CHD anatomy and physiology. Data related to health care will only increase in ensuing years. Artificial intelligence and machine learning will be critical in optimizing the use of such data in the care of patients. In the near future, real-time analysis of patient-specific data will alert physicians of impending physiological compromise before hemodynamic change is apparent to the patient or the physician. Artificial intelligence and machine learning will also become fundamental in the diagnosis of conditions. Remote monitoring, both for perioperative care that decreases hospital stays and in the intermittent or continuous monitoring and management of chronic conditions, will become routine.

In the second part of this review paper, we are going to evaluate the diagnostics in COVID-19 cardiac patients.

Coronavirus disease 2019 (COVID-19) exerts an unprecedented global impact on public health and health care delivery. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 has reached pandemic levels since March 2020 (20). Patients with cardiovascular (CV) risk factors and established CVD represent a vulnerable population when suffering from COVID-19, and have an increased risk of morbidity and mortality. Severe COVID-19 infection is associated with myocardial damage and

cardiac arrhythmia. Common cardiac complications in SARS were: hypotension, myocarditis, arrhythmias, and sudden cardiac death (SCD) (21, 22). The European Society for Cardiology evaluated this global health problem and gave the *ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic*, so in the following lines are some diagnostic criteria for cardiovascular diseases in scenario of Covid 19 (23).

Diagnostic workup during SARS infection revealed electrocardiographic changes, sub-clinical left ventricular (LV) diastolic impairment and troponin elevation. Monitoring of cardiac toxicity of antiviral drugs is recommended. SARS-CoV-2 not only causes viral pneumonia but has major implications for the CV system. Patients with CV risk factors including male sex, advanced age, diabetes, hypertension and obesity as well as patients with established CV and cerebrovascular disease have been identified as particularly vulnerable populations with increased morbidity and mortality when suffering from COVID-19. Moreover, a considerable proportion of patients may develop cardiac injury in the context of COVID-19 which portends an increased risk of in-hospital mortality. Aside from arterial and venous thrombotic complications presenting as acute coronary syndromes (ACS) and venous thromboembolism (VTE), myocarditis plays an important role in patients with acute heart failure (HF). A wide range of arrhythmias has been reported to complicate the course of COVID-19 including potential pro-arrhythmic effects of medical treatment targeted at COVID-19 and associated diseases. *Strategies for Diagnosing SARS-CoV-2*: Diagnosis of COVID-19 relies on a combination of epidemiological criteria (contact within incubation period), presence of clinical symptoms as well as laboratory testing (nucleic acid amplification tests) and clinical imaging based tests. Antibody and SARS-CoV-2 antigen based enzyme-linked immunosorbent assay (ELISA) tests are under development and are not yet fully validated. Widespread testing proves efficient in the containment phase of the epidemic. Quality of sample collection (deep nasal swab) and transport (time) to laboratories are essential to avoid false negative outcomes. Lung computed tomography (CT) imaging may be used as a diagnostic test in COVID 19.

Diagnosis of Cardiovascular Conditions in COVID-19 Patients: Chest pain and breathlessness is a frequent symptom in COVID-19 infection. Chronic and acute coronary syndrome presentations can be associated with respiratory symptoms. In COVID-19 patients with impaired end-organ perfusion at risk of cardiogenic shock (CS) (e.g., large acute myocardial infarction

[AMI]), consider also sepsis as possible or mixed aetiology. Myocarditis should be considered as precipitating cause of CS. The same ECG diagnostic criteria for cardiac conditions apply in patients affected by the SARS-CoV-2 infection and in the general population. *Biomarkers:* Cardiomyocyte injury, as quantified by cardiac troponin T/I concentrations, and haemodynamic stress, as quantified by B-type natriuretic peptide (BNP) and N-terminal B type natriuretic peptide (NT-proBNP) concentrations, may occur in COVID-19 infections as in other pneumonias. The level of those biomarkers correlates with disease severity and mortality; Cardiac troponin T/I and BNP/NT-proBNP concentrations should be interpreted as quantitative variables. D-Dimers quantify activated coagulation, a prominent feature in COVID-19. Due to the central role of endothelitis and VTE /Venous thromboembolism/ in COVID-19, serial measurements of D-dimers may help in the selection of patients for VTE-imaging and/or the use of higher than prophylactic doses of anticoagulation. *Cardiac Troponin I/T:* COVID-19 is a viral pneumonia that may result in severe systemic inflammation and ARDS (Acute respiratory distress syndrome), and both conditions have profound effects on the heart. As a quantitative marker of cardiomyocyte injury, the concentrations of cardiac troponin I/T in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease and the acute injury related to COVID-19 (23, 24, 25). *B-Type Natriuretic Peptide/ N-Terminal B-Type Natriuretic Peptide:* BNP/NT-proBNP as quantitative biomarkers of haemodynamic myocardial stress and HF (Heart failure) are frequently elevated among patients with severe inflammatory and/or respiratory illnesses (26, 27). While experience in patients with COVID-19 is limited, very likely the experience from other pneumonias can be extrapolated to COVID-19. Dimers should be monitored routinely. In particular, elevations of D-Dimers have been associated with poor outcome (28). *Non-Invasive Imaging:* In patients with suspected or confirmed COVID-19, contamination from patient to other patients, imagers and imaging equipment should be prevented. Imaging studies should be performed in patients with suspected or confirmed COVID-19 only if the management is likely to be impacted by imaging results. Re-evaluate which imaging technique is best for patients both in terms of diagnostic yield and infectious risk for the environment. The imaging protocols should be kept as short as possible. *Transthoracic (TTE) and Transoesophageal Echocardiography (TEE).* Performing transthoracic, transoesophageal and stress echocardiograms should be avoided in patients in

which test results are unlikely to change the management strategy. TEE carries increased risks of spread of COVID-19 due to exposure of HCP (Healthcare personnel) to aerosolization of large viral load and should not be performed if an alternative imaging modality is available. In COVID-19 infected patients, the echocardiogram could be performed focusing solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and the HCP performing the test. Point of care focused ultrasound (POCUS), focused cardiac ultrasound study (FoCUS) and critical care echocardiography performed at bedside are effective options to screen for CV complications of COVID-19 infection. *Echocardiography* can be performed bedside to screen for CV complications and guide treatment. POCUS, FoCUS and critical care echocardiography are probably the preferred modalities to image patients with COVID-19. Limited evidence exists for the use of lung ultrasound to differentiate acute respiratory distress syndrome - ARDS (single and/or confluent vertical artefacts, small white lung regions) from HF. The presence of dilated right ventricle and pulmonary hypertension may indicate contrast CT to rule out PE (Pulmonary embolism). In COVID-19 infected patients, echocardiography should focus solely on the acquisition of images needed to answer the clinical question in order to reduce patient contact with the machine and HCP. *Cardiac CT* should be performed when there is a potential impact on clinical management, including evaluation of symptomatic suspected CAD (Coronary artery disease), acute symptomatic heart valve dysfunction, left ventricular assist device (LVAD) dysfunction, PE pulmonary embolism, and urgent structural intervention (29). Cardiac CT is preferred to TEE to rule out the presence of intracardiac thrombus. In patients with acute chest pain and suspected obstructive CAD, CCTA (Coronary computed tomography angiogram/angiography) is the preferred non-invasive imaging modality since it is accurate, fast and minimizes the exposure of patients. In patients with respiratory distress, lung CT is recommended to evaluate imaging features typical of COVID-19 and differentiate from other causes (HF, PE) (30). However, it should not be used to screen for or as a first-line test to diagnose COVID-19 and should be reserved for hospitalized patients. A dedicated CT scanner for patients with suspected or confirmed COVID-19 is preferred. As in other imaging modalities, local standards for prevention of virus spread and protection of personnel should be followed.

Nuclear cardiology should be performed only in specific indications and when no other imaging modalities can be performed. The shortest duration

of scan time and exposure should be used. Standard dose imaging with rapid protocols of data acquisition are recommended. Positron emission tomography (PET) minimizes the acquisition times. *Cardiac Magnetic Resonance* (CMR) protocols are focused to address the clinical problem.

Performance of *exercise testing* (either conventional, Echo or nuclear) has major limitations in the COVID-19 era. During exercise, the patient increases respiration rate and the amount of aerosol or droplets production, even if wearing a surgical mask (that could strongly affect his/her exercise capacity). This problem is further increased since rooms of outpatient clinics are rarely large and well aerated. Performance of exercise testing is discouraged in COVID-19 suspect or positive patients and, in general, in every patient in COVID-19 epidemic or potentially epidemic areas. Alterative diagnostic methods for CAD not requiring exercise should be used as an alternative to exercise testing whenever possible. The presence of COVID-19 infection should not preclude a systematic search for CV events, including ACS (Acute coronary syndrome). COVID-19 infection-related injury should be kept in mind as differential diagnosis. Other manifestations and complications of COVID-19 infection mimicking heart disease should also have been ruled out. No doubt the use of complex tools to refine our diagnostic accuracy will lead us toward the delivery of more sophisticated or patient-specific prevention strategies or therapies.

Conclusion

As a part of lifelong learning process for all professionals in cardiovascular medicine, the imperative is to have continuity of reviewing novelties, with research results in order to treat patient according to best practices and evidence-based medicine. All professionals in cardiovascular medicine, as a part of lifelong learning process, have the continuous imperative in reviewing novelties, with resulting data from numerous researches in order to treat all patients according to best practices and evidence-based medicine, especially on this journey through corona pandemic.

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NOVOSTI U DIJAGNOSTIČKOJ KARDIOLOGIJI

Apstrakt

Kardiovaskularna medicina je područje kliničke prakse s kontinuirano brzim širenjem znanja, smjernica, najboljih praksi i novih tehnologija u kardiovaskularnoj medicini odraslih, kao i u dječjoj kardiološkoj medicini. Kardiovaskularne bolesti (KVB) su vodeći uzrok smrtnosti u svijetu i uzrokuju velike troškove za zdravstveni sektor i ekonomiju. Indeksi kardiovaskularnog snimanja imaju značajan utjecaj na prevenciju, dijagnozu i liječenje srčanih bolesti. Napredne tehnologije snimanja dramatično su poboljšale našu sposobnost otkrivanja i liječenja kardiovaskularnih bolesti u ranoj fazi. Multimodalne tehnike snimanja: ehokardiogram, kompjuterska tomografija srca, snimanje magnetnom rezonancom, simulacijski 3D modeli, umjetna inteligencija se koriste sve češće, jer se njihova korisnost sve više cijeni.
Globalni utjecaj koji koronavirusna bolest 2019 (COVID-19) ima na javno zdravlje i pružanje zdravstvene njege je bez presedana. Teški akutni respiratorni sindrom koronavirus 2 (SARS-CoV-2) koji uzrokuje COVID-19 dosegao je nivo pandemije u martu 2020. godine. Pacijenti s kardiovaskularnim (CV) faktorima rizika i ustanovljenim KVB-om predstavljaju ranjivu populaciju od COVID-19 te imaju povećan rizik od morbiditeta i mortaliteta. Teška COVID-19 infekcija povezuje se s oštećenjem miokarda i srčanom aritmijom. Dijagnostički pregledi tokom SARS infekcije otkrili su elektrokardiografske promjene, subkliničko dijastoličko oštećenje lijeve ventrikule (LV) i povišenje troponina.
Svi stručnjaci u kardiovaskularnoj medicini, u sklopu procesa cjeloživotnog učenja, imaju kontinuirani imperativ praćenja noviteta, uključujući rezultate brojnih istraživanja, kako bi svi pacijenti bili liječeni prema najboljim praksama i medicini zasnovanoj na dokazima, posebno na ovom putu kroz pandemiju koronavirusa.

Ključne riječi: dijagnostika, kardiologija, ažuriranje

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DIAGNOSTICS OF PREVENTABLE DISEASES IN CARDIOLOGY

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Abstract

Despite many efforts to diagnose and treat preventable cardiovascular diseases (CVD), more specifically to detect known risk factors, these diseases continue to be the leading cause of morbidity and mortality. Bosnia and Herzegovina belongs among the high-risk countries with standardized death rate (SDR) of 385 per 100 000 inhabitants in 2018. Two leading causes of death are acute myocardial infraction, with rate around 90 deaths per 100 000 inhabitants and stroke with the rate around 80 deaths per 100 000 inhabitants in one year. Both incidents are preventable. Digital interventions are necessary for strengthening of the healthcare system. Benefits of eHealth could be seen in transmission of customized health information for different audiences: transmission of health-event alerts to a specified population group; transmission of health information based on health status or demographics; alerts and reminders to clients; transmission of diagnostic results (or of the availability of results) or even notifications and reminders for appointments, medication adherence, or follow-up services. Successful implementation of digital health requires multidisciplinary approaches, from mass dissemination of recommendations through public health education programs directly in the field, to clinical treatments for patients. All this requires the involvement of numerous actors, from the strategic to the operational level of management within the healthcare system in the country.

Key words: Cardiac disease, prevention, digital health

Introduction

Despite many efforts to diagnose and treat preventable cardiovascular diseases (CVD), more specifically to detect known risk factors, these diseases continue to be the leading cause of morbidity and mortality. Bosnia and Herzegovina belongs among the high-risk countries. Based on information of Public Health Institute of Federation of Bosnia and Herzegovina, standardized death rate (SDR) for cardiovascular diseases is 385 per 100,000 inhabitants (1). In contrast, in the European Union, yearly deathrate due to the cardiovascular diseases is 315 per 100,000 inhabitants (2). Access to digital information and communication has an increasing importance in both the work of healthcare professionals and in patients' everyday life and has transformed what we do and how we carry out activities. It changes the way in which healthcare is delivered, how information is exchanged within and between organizations and how patients and other actors access and manage information (3). Electronic health (eHealth) — technology to support health, well-being, and healthcare — can offer many benefits, such as increased quality of care, easily accessible healthcare, and increased self-management (4). Digital medicine (also called telemedicine or telehealth) and eHealth form a growing contemporary field in primary health care hastened by the Covid-19 pandemic. According to an EU-report, 96% of GPs in Europe used electronic health records in 2018 [5]. The Nordic countries together with Estonia, Spain and the UK have adopted eHealth to a high degree and most patients in Denmark, Estonia, Finland, Sweden and the UK can view their medical records and test results electronically [6].

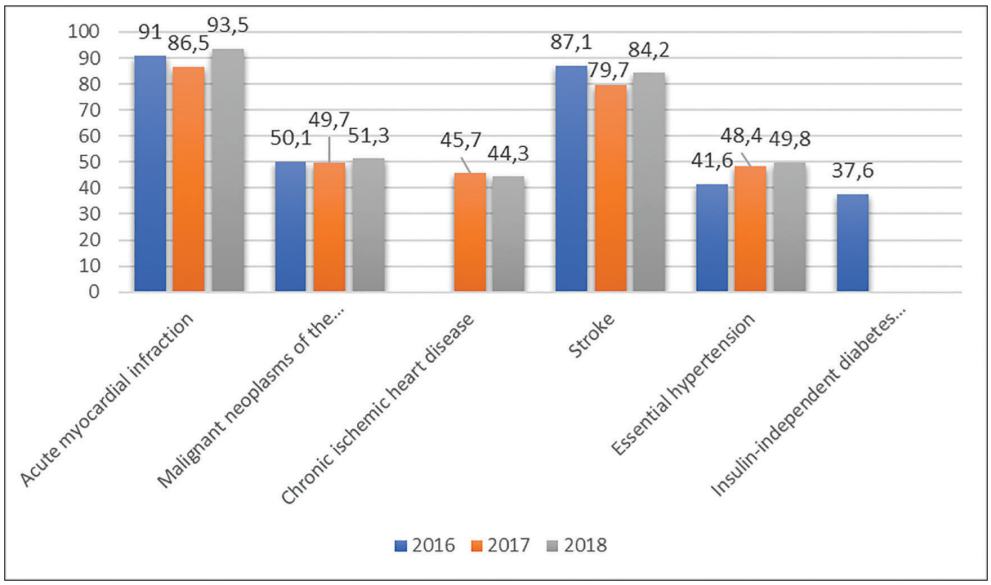
Aim of our paper was to show the importance of implementing new technologies in health system which could lead to timely and adequate reactions of the competent health authorities.

Methods and materials

The authors used official data from the Federation of Bosnia and Herzegovina, the European Union and the World Health Organization to present the importance of projects focused on the prevention of cardiovascular diseases. The possibilities of using digital technologies are a combination of published official materials of the World Health Organization and the personal views of the authors.

Results and discussion

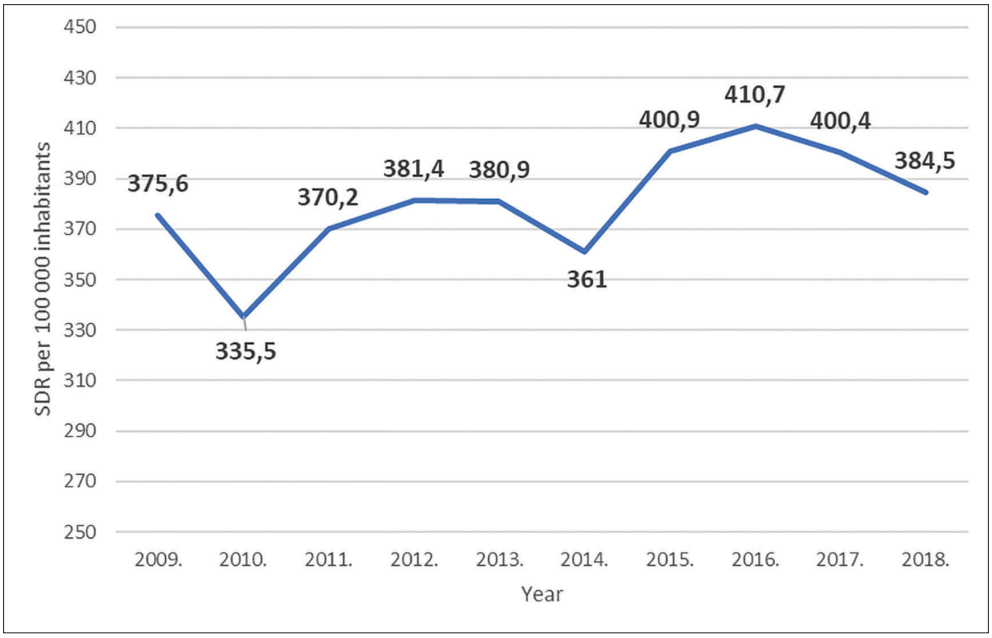
Cardiovascular disease SDR was at the peak in year 2016, with SDR = 410,7/100,000 inhabitants. It is slowly declining since that period. At the same time, chronical respiratory incidence is increasing, along with the deaths caused by it. Five leading diseases as causes of death in Federation of Bosnia and Herzegovina in period of 2016 – 2018 are shown in Graph 1.



Graph 1. Five leading diseases as causes of death in the Federation of BiH Rates are calculated per 100,000 inhabitants in period 2016 – 2018

As seen in the Graph 1, two leading causes of death are acute myocardial infarction, with rate around 90 deaths per 100 000 inhabitants, and stroke with the rate around 80 deaths per 100 000 inhabitants per year. Both incidents are preventable.

These rates are even higher in male population, with the acute myocardial infarction deathrate reaching a peak (108/100,000) in year 2018. In contrast, in female population, mortality rate was 79 per 100 000 inhabitants in the same year. In male population the rate of malignant neoplasms is also increasing over the period of three years, while rate of deaths caused by stroke is around 75 per 100,000 people. Standardized death rates from cardiovascular diseases are showing wave like pattern (Graph 2).



Graph 2: SDR from cardiovascular diseases per 100,000 inhabitants

As seen from previous graphs, management of preventable diseases in cardiology should lead to the reduction of deaths from these causes. According to published WHO research, the main barriers to adequate management of preventable diseases in cardiology are: lack of unique clinical guides; inadequate training of health workers in the management of CVD in the Primary Health Care; inadequate access of patients to health services; insufficient use of modern health technologies (7). Digital interventions are necessary for strengthening of the healthcare system. What is proving inevitable in the current moment and in the modern environment is the proactive role of the healthcare system in the field of digital health as a support to cardiovascular health in Europe, which is included in the current action plan of the European Society of Cardiology (ESC). The term digital health stems from eHealth, which is defined as "the use of information and communications technology in support of health and health-related fields" (8). Mobile health (mHealth) is a subset of eHealth and is defined as "the use of mobile wireless technologies for health." More recently, the term digital health was introduced as "a broad umbrella term encompassing eHealth (which includes mHealth), as well as emerging areas, such as the use of advanced computing sciences in 'big data', genomics and artificial intelligence."

The future is focused on the digital transformation of healthcare and the need for efficient and safe innovation in order to improve the efficiency of health practices, and thus improving the diagnosis of preventable diseases, including preventable cardiac diseases. The development of innovative solutions to ensure people's access to prevention and treatment of CVD across Europe is a necessary and urgent priority. There is need for promoting innovation and modernizing research regulations to improve: Earlier recognition of cardiovascular disease; Repair of the heart and blood vessels; Knowledge on the interaction between CVD and other disorders; Treatment of chronic heart failure and atrial fibrillation. In primary prevention for example, mobile applications, text messaging and monitoring sensors for self-tracking, as well as online counselling, have the potential to identify people with high cardiovascular risk, and improve lifestyle management interventions to reduce cardiovascular risk. Supporting the digitalization of healthcare systems through the development of electronic health records and data repositories, as well as exploiting the potential of artificial intelligence, would play a key role in improving diagnosis and treatment of CVD. Benefits of eHealth could be seen in transmission of customized health information for different audiences: transmission of health-event alerts to a specified population group; transmission of health information based on health status or demographics; alerts and reminders to clients; transmission of diagnostic results (or of the availability of results) or even notifications and reminders for appointments, medication adherence, or follow-up services.

Conclusion

Successful implementation of digital health requires multidisciplinary approaches, from mass dissemination of recommendations through public health education programs directly in the field to clinical treatments for patients. All this requires the involvement of numerous actors, from the strategic to the operational level of management within the healthcare system in the country.

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DIJAGNOSTIKA BOLESTI KOJE SE MOGU SPRIJEČITI U KARDIOLOGIJI

Apstrakt

Uprkos mnogim naporima u dijagnosticiranju i liječenju kardiovaskularnih bolesti (KVB) koje se mogu spriječiti ili preciznije u otkrivanju poznatih faktora rizika, ove bolesti su i dalje vodeći uzrok morbiditeta i mortaliteta. Bosna i Hercegovina spada među zemlje visokog rizika sa standardiziranom stopom smrtnosti od 385 na 100.000 stanovnika u 2018. godini. Dva vodeća uzroka smrtnosti bili su akutni infarkt miokarda, sa stopom od oko 90 smrtnih slučajeva na 100.000 stanovnika i moždani udar sa stopom od oko 80 smrtnih slučajeva na 100.000 stanovnika u jednoj godini. Oba incidenta se mogu spriječiti. Neophodne su digitalne intervencije za jačanje zdravstvenog sistema. Prednosti eZdravstva (eHealth) mogu se vidjeti u prenošenju prilagođenih zdravstvenih informacija za različite publike: prenošenje upozorenja o zdravstvenim događajima određenoj grupi stanovništva; prenošenje zdravstvenih informacija na osnovu zdravstvenog stanja ili demografskih podataka; upozorenja i podsjetnici klijentima; prenošenje dijagnostičkih rezultata (ili informacija o dostupnosti rezultata) ili čak obavještenja i podsjetnika o terminima, pridržavanju terapijama ili popratnim uslugama. Uspješna implementacija digitalnog zdravlja zahtijeva multidisciplinarne pristupe, od masovnog širenja preporuka kroz obrazovne programe o javnom zdravlju direktno na terenu, do kliničkog liječenja pacijenata. Sve ovo zahtijeva uključivanje brojnih aktera, od strateškog do operativnog nivoa upravljanja unutar zdravstvenog sistema u državi.

Ključne riječi: kardiovaskularna bolest, sprečavanje, digitalno zdravlje

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ACHD - New Guidelines and Clinical Care Perspective
Professional paper

ADULT CONGENITAL HEART DISEASE – NEW GUIDELINES AND CLINICAL CARE PERSPECTIVE

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Abstract

To date, the prevalence of CHD worldwide is ~9 per 1000 newborns, with substantial geographic variation. The latest knowledge in the world for the last 50 years about their origin, diagnosis and therapy has contributed to their care. Since adult patients with CHD now present increasing numbers at advanced ages, including the elderly, the term grown-up CHD no longer appears appropriate and was therefore replaced with adult CHD (ACHD) according to the ESC guidelines published in 2020 year. Due to medical, surgical, and technological evolutions over the past decades, >90% of individuals who are born with CHD now survive into adulthood. ACHD represent a challenge for clinicians. Despite optimal medical and surgical treatment, many will experience a progressive decline in cardiopulmonary function leading to advanced heart failure. Severe ventricular dysfunction and/or pulmonary hypertension may not be amenable to corrective repair. Their early recognition and follow-up in adolescence will contribute to better care for these patients. Importantly, the care for ACHD patients is a lifelong process and requires advance care planning strategies.

Key words: Adult congenital heart disease, heart failure, pulmonary hypertension, infective endocarditis, sudden cardiac death.

Introduction

To date, the prevalence of CHD worldwide is ~9 per 1000 newborns, with substantial geographic variation. Congenital heart defects (CHD) are more common than those found in all age groups, including the fetus. The latest knowledge in the world for the last 50 years about their origin, diagnosis and therapy has contributed to their care. However, in underdeveloped countries, millions of children born with CHD do not have adequate diagnosis, therapy, or prevention.

Since 2006, The World Society for Pediatric and Congenital Heart Surgery has been promoting the care of children with CHD from fetus to adulthood, regardless of the economic status of patients, with recommendations for education, diagnostic and therapeutic care for all. Since 1970, more than 70 population epidemiological studies have been published worldwide with a questionnaire on genetics, sociodemographic, medical-obstetric data, exposure to environmental risks and drugs, risk assessment and prevention of heart defects. Since adult patients with CHD now present increasing numbers at advanced ages, including the elderly, the term grown-up CHD no longer appears appropriate and was therefore replaced with adult CHD (ACHD) according to the ESC guidelines published in 2020 year.

Methods and materials

A. Aetiology

Congenital heart defects are disorders of the anatomical structure or function of the heart and blood vessels, which are most often the result of impaired or stopped development of certain structures at the level of the embryonic or fetal phase. The exact cause of most congenital heart defects remains unknown. They are the result of the complex action of genetic and environmental factors. Knowing the aetiology is important for their prevention.

Chromosomal aberrations and gene mutations have been detected in less than 10% of congenital heart defects, whether they are isolated or associated with other genetic abnormalities in syndromes such as Down, Turner, Marfan, Noonan, Loeys-Dietz and others. There has been remarkable progress in understanding the genetic basis of cardiovascular malformations. Chromosome microarray analysis has provided a new tool to understand the genetic basis of syndromic cardiovascular malformations resulting from microdeletion

or microduplication of genetic material, allowing the delineation of new syndromes.

Enzyme deficiencies in fetal cells obtained by amniocentesis or biopsy of chorionic villi contribute to the prediction of defects, and fetal echocardiography can directly detect cardiovascular malformations during the so-called risk factors (family burden, mother's age, etc.). Teratogenic agents, which act especially during the embryonic development of the heart, have a role in the development of congenital heart defects in the first 3 months of pregnancy. They are divided into infectious, chemical and physical, and the most famous are rubella and maternal viral infections in general; drugs the mother takes, as well as heroin, cocaine, smoking, alcohol; then hypoxia, radiation, trauma, etc.

B. Classification of ACHD

The classification of congenital heart defects can be based on anatomical, functional (hemodynamic), radiological or other characteristics of defects that are often combined or complex. CHD can be classified as mild, moderate, or severe according to complexity. **(Table No. 1)**

Table No. 1. Classification of congenital heart disease complexity

MILD:
Isolated congenital aortic valve disease and bicuspid aortic disease
Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
Mild isolated pulmonary stenosis (infundibular, valvular, supravalvular)
Isolated small ASD, VSD, or PDA
Repaired secundum ASD, sinus venosus defect, VSD, or PDA without residuae or sequellae, such as chamber enlargement, ventricular dysfunction, or elevated PAP.
MODERATE: (Repaired or unrepaired where not specified; alphabetical order)
Anomalous pulmonary venous connection (partial or total)
Anomalous coronary artery arising from the PA
Anomalous coronary artery arising from the opposite sinus
Aortic stenosis - subvalvular or supravalvular
AVSD, partial or complete, including primum ASD (excluding pulmonary vascular disease)
ASD secundum, moderate or large unrepaired (excluding pulmonary vascular disease)
Coarctation of the aorta
Double chambered right ventricle
Ebstein anomaly
Marfan syndrome and related HTAD, Turner Syndrome

PDA, moderate or large unrepaired (excluding pulmonary vascular disease)
Peripheral pulmonary stenosis
Pulmonary stenosis (infundibular, valvular, supravalvular), moderate or severe
Sinus of Valsalva aneurysm/fistula
Sinus venosus defect
Tetralogy of Fallot – repaired
Transposition of the great arteries after arterial switch operation
VSD with associated abnormalities (excluding pulmonary vascular disease) and/or moderate or greater shunt
SEVERE: (Repaired or unrepaired where not specified; alphabetical order)
Any CHD (repaired or unrepaired) associated with pulmonary vascular disease (including Eisenmenger syndrome)
Any cyanotic CHD (unoperated or palliated)
Double-outlet ventricle
Fontan circulation
Interrupted aortic arch
Pulmonary atresia (all forms)
Transposition of the great arteries (except for patients with arterial switch operation)
Univentricular heart (including double inlet left/right ventricle, tricuspid/mitral atresia, hypoplastic left heart syndrome, any other anatomic abnormality with a functionally single ventricle)
Truncus arteriosus
Other complex abnormalities of AV and ventriculoarterial connection (i.e., crisscross heart, heterotaxy syndromes, ventricular inversion).

ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; CHD = congenital heart disease; HTAD = heritable thoracic aortic disease; LV = left ventricle/ventricular; PA = pulmonary artery; PAP = pulmonary artery pressure; PDA = patent ductus arteriosus; VSD = ventricular septal defect. Source: 2020 ESC Guidelines for the management of adult congenital heart disease. European Heart Journal, Volume 42, Issue 6, 7 February 2021, Pages 563-645,

The classification into defects without cyanosis and with cyanosis is common. Cyanosis is divided into defects with left-right shunt and without shunt. Defects with a shunt are further divided according to the level of communication between the systemic and pulmonary circulation, and defects without a shunt depending on whether they refer to the structures of the inflow or outflow trough the left or right heart. Cyanotic defects are divided into those with increased and reduced pulmonary flow, based on which the cause of cyanosis (mixing of arterial and venous blood or reduction of pulmonary flow) is clarified.

Congenital heart defects in adults include: atrial septal defect (ASD), atrial septal defect and anomalous pulmonary venous connection, ventricular septal defect (VSD), atrioventricular septal defect (AVSD), patent ductus arteriosus (PDA), left ventricular outflow tract obstruction (LVOTO), valvular

aortic stenosis, supravalvular aortic stenosis, subaortic stenosis, coarctation of the aorta (CoA), Aortopathies including Marfan syndrome, right ventricular outflow tract obstruction (RVOTO), Ebstein's anomaly, Tetralogy of Fallot, Pulmonary atresia with ventricular septal defect, transposition of the great arteries, congenitally corrected transposition of the great arteries (ccTGA), univentricular heart, patients after Fontan operation and coronary anomalies. To date, ~90% of patients with mild, 75% with moderate, and 40% with complex heart defects reach the age of 60 years.

The frequency of individual defects is different. Although over a hundred anomalies have been described, 85% are due to 8 congenital heart defects that also occur in adults: atrial septal defect, ventricular septal defect, patent ductus arteriosus, congenital aortic stenosis, aortic coarctation, pulmonary stenosis, tetralogy of Fallot, transposition of great arteries.

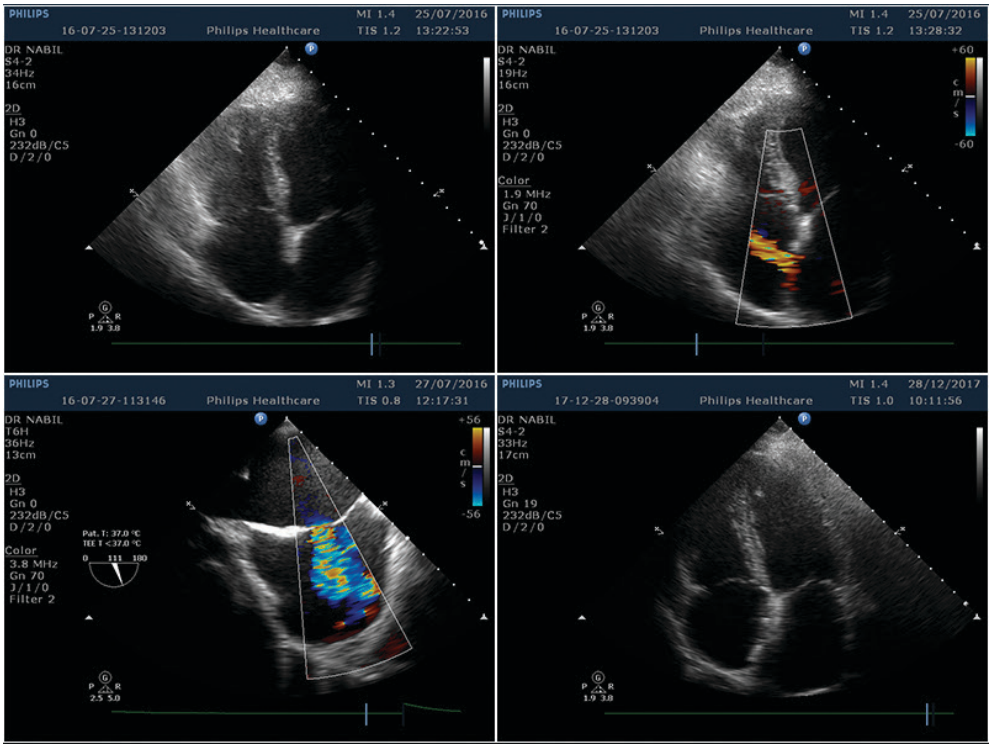

Figure 1. A secundum atrial septal defect (ASD) in 46 years old female patient with left-to-right shunt was confirmed by 2-dimensional transthoracic echocardiogram (TTE) (Panel A), 2-dimensional TTE color Doppler (Panel B). Transesophageal bicaval view with color Doppler (TEE) (Panel C) and TTE echocardiography of the final result after transcatheter closure with Amplatzer occluder (Panel D).

Secundum ASD (80% of ASDs; located in the region of the fossa ovalis and its surrounding). The ASD type secundum is the communication between the left and right atria placed lower towards the mitral valves. It is often associated with anterior mitral valve fissure and consequent mitral regurgitation (MR). Device closure has become the first choice for secundum defect closure, when feasible, based on the morphology (includes stretched diameter ≤38 mm and sufficient rim of 5 mm except towards the aorta).

Primum ASD [15%; synonyms: partial AV septal defect [atrioventricular septal defect (AVSD) with communication on the atrial level only], partial AV canal; located near the crux, AV valves are typically malformed, resulting in various degrees of regurgitation. The shunt volume depends on RV/LV compliance, defect size, and LA/RA pressure. If the defect is large, it burdens the pulmonary circulation and gives symptoms. It can be treated by surgical or catheter interventional treatment.

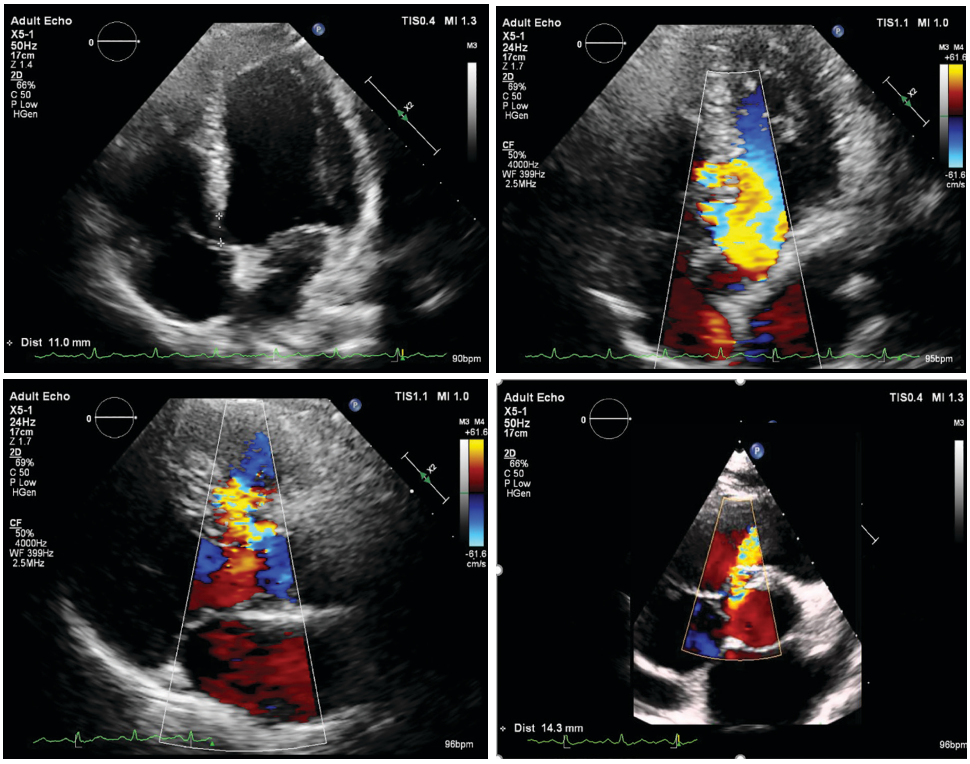

Figure 2. A perimembranous ventricular septal defect with small muscular VSD in 34 years old male with left - right shunt was confirmed by 2-dimensional transthoracic echocardiogram (TTE) (Panel A) and 2-dimensional TTE color Doppler (Panel B, C and D).

VSD is mostly diagnosed and, when indicated, treated before adulthood. Spontaneous closure is frequent in childhood. Several locations of the defect within the interventricular septum are possible, and these can be divided into four groups according to their location within the RV: perimembranous /paramembranous/subaortic/conoventricular (most common, ~80% of VSDs), muscular/trabecular (up to 15-20%), Outlet (with or without malalignment of the outlet septum) and Inlet/AV canal/AVSD type. Due to the increased blood flow on the left side, the pulmonary circulation is burdened. Surgical closure can be performed with low operative mortality (1–2%) and good long-term results. Transcatheter closure has become an alternative, particularly in residual VSDs, in VSDs that are poorly accessible for surgical closure, and in muscular VSDs that are located centrally in the interventricular septum.

Patent ductus arteriosus (PDA) is the persistent communication between the proximal left PA and the descending aorta just distal to the left subclavian artery. It can be associated with a variety of CHD lesions, however, in adults, it is usually an isolated finding. PDA originally results in L–R shunt and LV and LA volume overload. In adults, calcification of the PDA may cause a problem for surgical closure. Device closure is the method of choice, even if cardiac operations are indicated due to other concomitant cardiac lesions and can be successfully performed in the vast majority of adults with a very low complication rate.

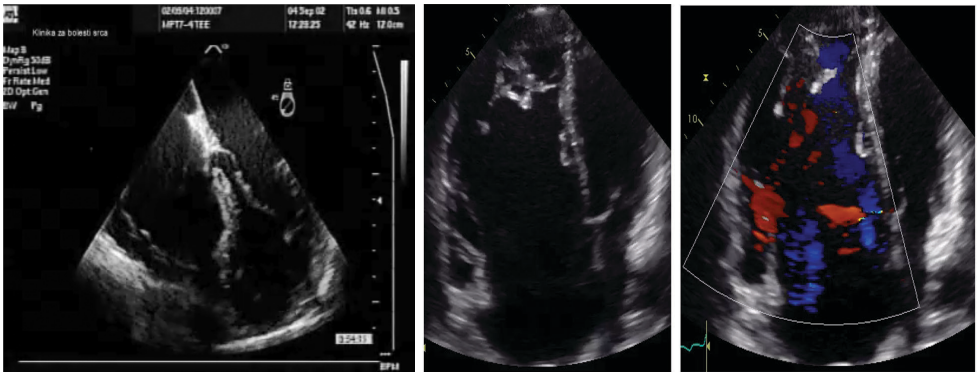

Figure 3. Ebstein's Anomaly with atrialization of the right ventricle in 56 years old female patient with history of supraventricular paroxysmal tachycardia and ischemic cerebrovascular insult.

Ebstein's anomaly is characterized by abnormally formed and apically displaced leaflets of the tricuspid valve. The anterior leaflet usually originates

at the annular level but is enlarged and sail-like, while the septal and posterior leaflets are displaced towards the RV apex and often tethered to the endocardium. Clinical symptoms determine the treatment. Conservative therapy can alleviate symptoms temporarily and create a beneficial basis for the following operation. Surgical repair remains challenging and should only be performed by surgeons with specific experience in this lesion.

CoA is considered as part of a generalized arteriopathy, and not only as narrowing of the aorta. It occurs as a discrete stenosis or as a long, hypoplastic aortic (arch) segment. Typically, CoA is located in the area where the ductus arteriosus inserts, and only in rare cases occurs ectopically (ascending, descending, or abdominal aorta). Associated lesions include bicuspid aortic valve (up to 85%), ascending aortic aneurysm, subaortic stenosis or supraoptic stenosis and (supra)mitral valve stenosis. Patients with CoA who reach adolescence demonstrate particularly good long-term survival up to age 60 years. The natural course may be complicated by left heart failure, intracranial haemorrhage (from berry aneurysm), infective endocarditis, aortic rupture/dissection, premature coronary and cerebral artery disease, and associated heart defects. (1,2,3.4.5.6)

C. Clinical signs

Due to medical, surgical, and technological evolutions over the past decades, >90% of individuals who are born with CHD, now survive into adulthood. As a result, the prevalence of CHD in the community has increased and now by far exceeds the number of children with CHD.

In congenital heart defects, anatomical changes cause functional changes in the heart and circulation, which further cause new anatomical changes and vice versa. They are interdependent, dynamic and constantly progressing, from the beginning to the end of life. Depending on the severity of the hemodynamic disorders, a number of defects are fatal before birth or immediately after birth. A significantly higher number of anomalies allow the development of the child, but with disorders (developmental delay, feeding dyspnoea, heart failure, etc.) that require correction in the earliest childhood or during adolescence. There are also defects with mild hemodynamic disorders and without them, which remain undiagnosed in childhood, and for quite a long time in adults until the appearance of problems due to complications of the defect, e.g., pulmonary hypertension and heart failure in the IV or V decade of life of a patient with a moderately large left-right shunt.

ACHD have an anamnestic long asymptomatic period, followed by a feeling of fatigue, shortness of breath on exertion, palpitations, arrhythmias, respiratory infections, and bacterial endocarditis.

Thanks to advances in early detection, medical and/or surgical treatment of defects and interventional cardiology, palliative/total correction of even complex congenital heart defects is performed at an earlier age, which allows the patient to live with fewer symptoms or without them. In the population of adults with congenital heart defects, more and more patients are operated on instead of patients with advanced functional and/or pathoanatomical disorders that prevent surgical intervention (except for transplantation). The condition of the pulmonary vascular bed and pulmonary hypertension play a decisive role in determining the operability of the defect, on which the clinical manifestations, course and prognosis of many defects also depend.

Pulmonary hypertension occurs due to increased blood flow and/or resistance in the pulmonary circulation. Increased pulmonary flow is given by defects with the left-right shunt. Increased pulmonary vascular resistance is most often the result of histopathological, obstructive changes in the small muscular arteries and pulmonary arterioles that occur in patients with pulmonary hypertension and/or increased pulmonary blood flow. Assessment of pulmonary hypertension and the condition of the pulmonary vascular bed is most often performed by catheterization of the heart. In addition to pressures, the magnitudes of blood flow and vascular resistance in the pulmonary and systemic bloodstream are determined and their relative ratios are calculated. In advanced cases, pulmonary angiography and lung biopsy are required.

Cyanosis: Central-type cyanosis in adults with congenital heart defect is a symptom and sign of hypoxemia due to the right-left shunt. Congenital cyanotic heart defects are less common, and cyanosis occurs much more often due to left-right shunt reversal in unoperated patients with initially cyanotic defect (Eisenmenger's syndrome due to a large interventricular septal defect, atrioventricular septal defect or open arterial canal).

Erythrocytosis is a physiological response to hypoxemia. Increased erythrocyte mass (haematocrit) and total blood volume are features of polycythaemia in patients with right-left shunt. Polycythaemia itself has side effects: thrombosis, embolism, bleeding. Thromboembolic complications and symptoms such as headache, dizziness, fatigue, numbness of the fingers, are caused by increased blood viscosity due to high haematocrit (Hct> 60%). Bleeding

is a consequence of haemostasis disorders, due to impaired platelet function and abnormalities in the coagulation and fibrinotic system.

Infective endocarditis is a common complication in patients with congenital heart defects, and routine antibiotic prevention is mandatory in all non-operated patients, as well as in most patients after defect correction. Patients are especially at risk after the implantation of valves (artificial, heterograft or homograft) and "conduit", so in these cases, parenteral administration of a combination of antibiotics is recommended. (1,2,9,11,12,13,14,15,17)

D. Diagnostic tools

The diagnosis is made by clinical examination, ECG, X-ray of the lungs and heart, biomarkers, echocardiography, Cardiac magnetic resonance imaging (CMRI), Computed tomography (CT), cardiopulmonary exercise testing (CPET) and cardiac catheterization**. Echocardiography** remains the first-line investigation and continues to evolve, with improved functional assessment using 3D echocardiography**. Cardiovascular Magnetic Resonance Imaging (CMRI)** has become an essential facility in the specialist unit. It enables 3D anatomical reconstruction, which is not restricted by body size or acoustic windows and has rapidly improving spatial and temporal resolution. **Cardiovascular CT** has high spatial resolution and rapid acquisition time; it is particularly relevant for imaging the great vessels, coronary arteries, and collateral arteries, and for parenchymal lung disease. **Cardiopulmonary exercise testing** has an important role in the CHD population, in which quality of life and functional capacity are key measures of the success of intervention. Cardiac catheterization is mainly reserved for resolution of specific anatomical and physiological questions, or for intervention. **Different classes of biomarkers** have been reported to be associated with adverse events in the CHD population, including: neurohormones peptides [B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP)], markers of myocardial injury (high-sensitivity troponins) or inflammation marker (high-sensitivity C-reactive protein). (1,2,6,7,10,17)

D. Therapeutic consideration

Heart Failure: The development of heart failure is a common problem affecting 20 to 50% of the ACHD population and is a main cause of death. **Arrhythmias:** The entire spectrum of arrhythmias may be encountered in ACHD patients. Supraventricular arrhythmias: atrioventricular reentrant

tachycardia (AVRT), intraatrial reentrant tachycardia (IART), ectopic atrial tachycardia (EAT) and atrial fibrillation (AF). Ventricular arrhythmias: sustained ventricular tachycardia (SVT) & sudden cardiac death (SCD). Bradycardia: sinus node dysfunction (SND) and AV block. **Sudden cardiac death (SCD)** related to ventricular arrhythmia is of concern (7–26% of all deaths in adults). Although the incidence in the CHD population at large is relatively low (<0.1% per year), some defects place patients at higher risk, with occasional disease-specific substrates and risk factors. Identifying patients at risk for SCD remains a challenge. **Pulmonary hypertension** is an important prognostic factor in patients with CHD, requiring particular attention in pregnancy or prior to reparative cardiac or other major surgery. Sudden cardiac death and risk stratification. **Cardiac surgery** in ACHD patients deserves special attention. Even small operations can carry a high risk. The need for personalized risk assessment, understanding the specific anatomy and haemodynamics, experience with CHD surgery or redo surgery, and special requirements in intensive care units are factors that determine short- and long-term outcomes. **Catheter interventions:** The most frequent percutaneous interventions are closure of shunt lesions (in particular secundum-type ASD, rarely VSD, and persistent arterial duct), fistula, or unusual collaterals; balloon dilatation of the pulmonary valve and valved grafts; balloon dilatation and/or stenting of narrowed great vessels [e.g. (re-coarctation of the aorta (CoA) and pulmonary arterial stenosis]; and transcatheter pulmonary valve implantation (TPVI). **Infective endocarditis:** The risk of infective endocarditis in ACHD patients is higher than in the general population, with marked variation between lesions. **Antithrombotic treatment:** It is known that patients with ACHD are at increased risk of thromboembolic events. **Management of cyanotic patients:** cyanosis caused by R–L shunt due to an anatomical communication between the systemic and pulmonary circulation at the atrial, ventricular, or arterial level. Cyanotic patients are complex and must be followed by an ACHD specialist. Multimodality imaging is key for adequate assessment of overall anatomy and ventricular and valvular function, and quantification of blood flow, including perfusion distribution. Special structural and organizational healthcare requirements are necessary to meet the needs of ACHD patients. (1,2,3,9,10,11)

Future directions

The main unmet needs in adult congenital heart disease are: 1. Increase in the number of randomized controlled trials. 2. Advanced care of heart failure in ACHD (Mechanical assist devices, transplant in complex CHD). 3. Cardiac resynchronization therapy in complex ACHD. 4. Leadless pacing. 5. Primary prevention of sudden cardiac death in patients with systemic right ventricle or single ventricular physiology. 6. Targeted therapies for pulmonary hypertension in Fontan patients. 7. RCTs for novel therapeutic agents in pulmonary hypertension associated with CHD. 8. Drug therapies in patients with failing systemic right ventricle or single ventricle. 9. Direct oral anticoagulants in ACHD patients. 10. Implementation of AI for better assessing systemic right ventricular or singe ventricle failure. 11. Development of validated prognostic models. 12. Omics-based personalized healthcare. There is a need for specialist ACHD centres worldwide. Staff requirements for specialist ACHD centres include adult/paediatric cardiologist with ACHD certification, ACHD imaging specialist (certified in TTE/TOE, CMR, CCT), congenital interventional cardiologist, CHD surgeon, anaesthesiologist with CHD experience and expertise, specialist nurse, invasive electrophysiologist with ACHD experience, pulmonary vascular disease expert, clinical geneticists, psychologist, social worker and palliative care team. (3,1,2)

Conclusion

ACHD represent a challenge for clinicians. Their early recognition and follow-up in adolescence will contribute to better care of these patients. The vast majority of patients survive into adulthood and their profile in terms of comorbidities has changed. Organization of tertiary and nontertiary care, collaboration at national and international level, randomized controlled trials and implementation of novelties, such as research based biobanking, e-health and artificial intelligence should all be employed to meet their healthcare needs. Importantly, the care for ACHD patients is a lifelong process and also requires advance care planning strategies.

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UROĐENE SRČANE BOLESTI ODRASLIH - NOVE SMJERNICE I PERSPEKTIVE KLINIČKE NJEGE

Apstrakt

Trenutna prevalencija urođenih srčanih mana (USM, eng. CHD) u svijetu je ~9 na 1000 novorođenčadi, sa značajnim geografskim varijacijama. Najnovija svjetska saznanja u posljednjih 50 godina o njihovom porijeklu, dijagnozi i terapiji doprinijela su njezi. Budući da danas ima sve više odraslih pacijenata s urođenim srčanim manama čak i u poodmakloj dobi, uključujući duboku starost, pojam "grown-up CHD" više se ne čini prikladnim i stoga je zamijenjen pojmom "adult CHD" (ACHD) prema smjernicama ESC-a objavljenim 2020. godine. Zbog medicinskog, hirurškog i tehnološkog napretka u posljednjim decenijama, >90% pojedinaca koji su rođeni s USM sada preživljavaju i u odraslu dob. ACHD predstavljaju izazov za kliničare. Uprkos optimalnom medicinskom i hirurškom liječenju, mnogi će doživjeti progresivno smanjenje kardiopulmonalne funkcije što dovodi do uznapredovale srčane insuficijencije. Teška ventrikularna disfunkcija i/ili plućna hipertenzija možda neće biti podložne korektivnim intervencijama. Njihovo rano prepoznavanje i praćenje u adolescenciji doprinijet će boljoj skrbi za ove pacijente. Važno je istaknuti da je briga o pacijentima s ACHD-om doživotni proces i zahtijeva unaprijed planirane strategije njege.

Ključne riječi: urođena srčana mana kod odraslih, zatajenje srca, plućna hipertenzija, infektivni endokarditis, iznenadna srčana smrt

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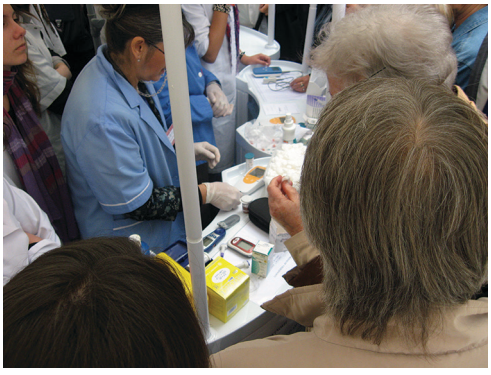


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