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Klasifikacija i klinički značaj kardiomiopatija

Classification and clinical importance of cardiomyopathies

Danijel Planinc*
Klinički bolnički centar Sestre milosrdnice, Zagreb, Hrvatska
University Hospital Centre Sestre milosrdnice, Zagreb, Croatia

U ovom broju *Kardio lista,* u okviru Almanaha 2011. Elliot i Mohiddin, objavljuju odličan pregledni članak o najnovijim dostignućima i spoznajama dijagnostike, patogeneze i liječenja, a posebice genomike i genetike kardiomiopatija.[1] Smatrao sam da se u Uvodniku treba osvrnuti na postojeće definicije, klasifikacije, opća obilježja i klinički značaj najčešćih oblika bolesti.

Kardiomiopatije su bolesti srčanog mišića karakterizirane progresivnim tijekom, često s dugotrajnom i neprepoznatom asimptomatskom fazom. Jedna su od najsloženijih, najinteresantnijih i najintrigantnijih grupa kardijalnih bolesti. Osim nekoliko iznimaka, histološki se nalazi hipertrofija kardiomiocita, nekroza i/ili fibroza. Simptomi i znaci bolesti u najvećeg broja bolesnika posljedica su razvoja disfunkcije lijeve ili obje klijetke, često s progresijom do manifestnog zatajivanja srca (ZS) što u većine bude i uzrok smrti.[2]

Moju prvu bolesnicu s dilatacijskom kardiomiopatijom, mladu ženu u dobi od 19 godina, liječio sam 1981. god., kada se ta bolest općenito rijetko dijagnosticirala i kada su među hospitaliziranim bolesnicima uglavnom prevladavali oni sa stečenim valvulnim ili prirođenim srčanim greškama. Tijekom proteklih 30 godina na Odjelu Kardiologije II Kliničkog bolničkog centra *Sestre milosrdnice* hospitalizirano je preko 3.000 bolesnika s primarnim i sekundarnim kardiomiopatijama. Kardiomiopatije danas nisu rijetke, a postignut je i veliki napredak u razumijevanju njihove patogeneze i načinima liječenja. Nažalost, bolest se i dalje često otkriva u uznapredovaloj fazi kada ima lošu prognozu.

Klasifikacije

Budući su kardiomiopatije uzrokovane brojnim patološkim procesima s još uvijek nedovoljno poznatim mehanizmima, njihova je klasifikacija teška. U proteklih 30 godina načinjen je niz različitih klasifikacija, ali neizbježna manjkavost svake je značajno preklapanje različitih grupa i oblika bolesti. Termin "kardiomiopatija" prvi je upotrijebio Brigden 1957. god., a o kliničkim obilježjima bolesti među prvima je pisao Goodwin sa suradnicima 1961. god.[3-4]

Svjetska zdravstvena organizacija (SZO) donijela je 1980. god. prvu klasifikaciju kardiomiopatija definirajući ih kao bolesti srčanog mišića nepoznatog uzroka i podijelivši ih na temelju morfološko-patofizioloških obilježja na dilatacijsku, hipertrofijsku i restrikcijsku kardiomiopatiju[5]. Ta se klasifikacija, zbog svoje jednostavnosti, zadržala u dnevnoj kliničkoj

In this issue of *Kardio list*, Elliott and Mohiddin have published in the Almanac 2011 an excellent review article on the latest achievements and knowledge of diagnostics, pathogenesis and treatment, especially genomics and genetics of cardiomyopathies.[1] I thought that the Editorial should address the existing definitions, classifications, general features and clinical significance of the most common types of the disease.

Cardiomyopathies are the heart muscle diseases characterized by progression, often with a long and unidentified asymptomatic phase. They are one of the most complex, interesting and intriguing group of heart diseases. Apart from a few exceptions, histologically we distinguish between hypertrophy of cardiomyocytes, necrosis and/or fibrosis. Symptoms and signs of the disease in the majority of patients are the consequence of the development of dysfunction of the left or both ventricles, often accompanied by progression to manifest heart failure (HF) which is in the majority of patients a cause of death.[2]

My first patient, a young woman aged 19, with dilated cardiomyopathy was treated by me in 1981, when the disease was rarely diagnosed in general, and when mainly patients with acquired valvular or congenital heart defects prevailed among hospitalized patients. Over the past 30 years at the Department of Cardiology II, of the University Hospital *Sestre milosrdnice* there were over 3000 patients with primary and secondary cardiomyopathies hospitalized. Cardiomyopathies are not rare today, and also great progress has been made in understanding their pathogenesis and treatment options. Unfortunately, the disease is still often discovered in an advanced stage when the disease prognosis is bad.

Classifications

Since cardiomyopathies are caused by a number of pathological processes with insufficiently known mechanisms, it is hard to classify cardiomyopathies. In the past 30 years, a number of different classifications have been made, but an inevitable shortcoming of every classification is a significant overlap of various groups and types of the disease. The term "cardiomyopathy" was first used by Brigden in 1957, while one of the first experts who wrote about clinical features of the disease were Goodwin et al in 1961.[3-4]

In 1980, World Health Organization (WHO) adopted the first classification of cardiomyopathies defining them as a heart muscle disease of unknown cause and dividing them accor-

praksi sve do danas i u nju se često, iako nepravilno, uvrštavaju srčane bolesti sličnih fenotipova, a različitih uzroka, od kojih su mnogi danas dobro poznati. Nesuglasice i nejasnoće oko definicije i klasifikacije kardiomiopatija i dalje traju. Mnoga stanja očituju se kao jedan, a s vremenom progrediraju u drugi oblik kardiomiopatije. Hipertenzivna bolest može npr. početi s hipertrofijom lijeve klijetke, a kasnije progredirati u dilataciju. Neke bolesti, kao npr. sarkoidoza srca, mogu imati dilatacijski ili restrikcijski fenotip.

Većim razumijevanjem etiologije i patogeneze, postajalo je sve teže razlikovati kardiomiopatije od specifičnih bolesti srčanog mišića te su SZO i Međunarodno društvo i Federacija kardiologije (WHO/ISFC) 1995. god. definirali kardiomiopatije kao bolesti miokarda udružene s disfunkcijom srca, uvrstivši među specifične upalnu kardiomiopatiju, histološki definiranu kao miokarditis s izraženom disfunkcijom srca. Virusna kardiomiopatija definirana je kao perzistencija virusa u miokardu dilatiranog lijevog ventrikula (LV) bez znakova upale. Aritmogena displazija desne klijetke i restrikcijska kardiomiopatija dodane su u primarne kardiomiopatije, a nekompaktni lijevi ventrikul u neklasificirane oblike bolesti. Sekundarni oblici kardiomiopatija koji su u klasifikaciji iz 1980. god. nazvani "specifične bolesti srčanog mišića" prozvani su "specifične kardiomiopatije" i u tu je skupinu dodan miokarditis. Termin specifične kardiomiopatije odnosio se na zahvaćenost srčanog mišića u sklopu specifičnih srčanih ili sistemskih bolesti. Nažalost, taj koncept je preširok i često je uključivao ishemijsku, valvulnu i hipertenzivnu bolest, što je glavni nedostatak te podjele.[6]

Etiološka klasifikacija je dobra, ali ne i savršena, jer bolesti sa sličnim genotipom mogu imati različite fenotipove i patogenezu i obrnuto. Idealna klasifikacija koja bi zadovoljila potrebe kliničara i bazičnih znanosti, teško će biti ostvariva. Razvoj sofisticiranih metoda pretraga, kao što su tehnike molekularne biologije, posebice tijekom proteklih 20 godina, omogućio je razumijevanje glavnih uzroka kardiomiopatija. To je prepoznato i u klasifikaciji koju je napravilo Američko kardiološko udruženje (AHA) 2006. god., koje je kadiomiopatije podijelilo na primarne i sekundarne, a definiralo kao heterogenu grupu bolesti miokarda udruženu s mehaničkom i/ili električnom disfunkcijom koja obično (ali ne uvijek) dovodi do neodgovarajuće hipertrofije i dilatacije klijetki, a posljedica je različitih uzroka koji su često nasljedni. Na osnovu genskih mutacija kardiomiopatije su tako podijeljene na citoskeletopatije (npr. dilatacijska, aritmogena displazija desne klijetke), sarkomiopatije (hipertrofijska, restrikcijska), poremećaje provođenja i kanalopatije (Sy. skraćenog i produljenog QT intervala, Sy. Brugada).[2,7-9] Ta je klasifikacija jedinstvena po tome, što je u primarne kardiomiopatije uključila i kanalopatije, poremećaje bez hemodinamske disfunkcije (***Tablica 1***).

ding to morphological and pathophysiological features into dilated, hypertrophic and restrictive cardiomyopathy[5]. This classification, due to its simplicity, has been kept in daily clinical practice until today and it often, though incorrectly, includes heart diseases with similar phenotypes, having various causes, of which many are well known today. Disagreements and misunderstandings in respect of the definition and classification of cardiomyopathies still persist. Many conditions are manifested as one, and eventually progress to other types of cardiomyopathy. For instance, hypertensive disease can start as left ventricular hypertrophy, and it can later progress to dilation. Some diseases such as cardiac sarcoidosis may have a dilated or restrictive phenotype.

Owing to better understanding of etiology and pathogenesis, it became more and more difficult to distinguish cardiomyopathies from specific heart muscle diseases, so in 1995 the WHO and the International Society and Federation of Cardiology (WHO/ISFC) defined cardiomyopathies as myocardial diseases associated with cardiac dysfunction, whereas inflammatory cardiomyopathy, histologically defined as myocarditis with pronounced cardiac dysfunction was included in specific cardiomyopathies. Viral cardiomyopathy is defined as the persistence of viruses in the myocardium of dilated left ventricle (LV) without signs of inflammation. Arrhythmogenic right ventricular dysplasia and restrictive cardiomyopathy are added to primary cardiomyopathies, while left ventricular non-compaction is added to unclassified types of the disease. Secondary types of cardiomyopathies which are in classification of 1980 called "specific heart muscle diseases" have been marked as "specific cardiomyopathies" with myocarditis added to this group. The term specific cardiomyopathies related to the affected heart muscle as a part of specific heart or systemic diseases. Unfortunately, this concept is too broad and it often included ischemic, valvular and hypertensive disease, which is the major drawback of this division.[6]

Etiological classification is good, but not perfect, because the diseases with similar genotype may have different phenotypes and pathogenesis and vice versa. The ideal classification that would meet the requirements of clinicians and basic sciences may hardly be made. The development of sophisticated search methods, such as molecular biology techniques, has especially during the past 20 years, enabled understanding of the main causes of cardiomyopathies. It is also recognized in the classification developed by the American Heart Association (AHA) in 2006 that divided cardiomyopathies into primary and secondary cardiomyopathies and defined them as a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction that usually (but not always) leads to inadequate hypertrophy and dilatation of the ventricles, resulting in a variety of causes that are often hereditary. On the basis of genetic mutations, cardiomyopathies are so divided into disease of the cytoskeleton (e.g. dilated, arrhythmogenic right ventricular dysplasia) diseases of the sarcomere /sarcomyopathies/ (hypertrophic, restrictive), conduction disorders and channelopathy (Short-QT and Long-QT syndrome, Brugada syndrome)[2,7-9] This classification is unique in the fact that it also included channelopathies in primary cardiomyopathies, disorders without hemodynamic dysfunction (***Table 1***).

Table 1.
Classification of cardiomyopathies.

A. Primary cardiomyopathies (predominantly involving the heart)

A.1. Primary-genetic
- Hypertrophic
- Arrhythmogenic right ventricular
- Left ventricular noncompaction
- Glycogen storage (PRKAG2, DANON)
- Conduction defects
- Mitochondrial myopathies
- Ion channelopaties

A.2. Primary-mixed (genetic and non-genetic)
- Dilated
- Restrictive (non-hypertrophied and non-dilated)

A.3. Primary-acquired
- Inflammatory (myocarditis)
- Stress-provoked (tako-tsubo)
- Peripartum
- Tachycardia induced
- Infants of insulin-dependent diabetic mothers

B. Secondary
- Infiltrative
- Storage
- Toxicity
- Endomyocardial
- Inflammatory (granulomatous)
- Endocrine
- Cardiofacial
- Neuromuscular/ Neurologic
- Nutritional deficiencies
- Autoimmune/ Collagen
- Electrolyte imbalance
- Consequences of cancer therapy

Modified from: Maron BJ, et al. Circulation. 2006;113:1807-16.

Europsko kardiološko društvo je, međutim, 2008. god. podijelilo kardiomiopatije na osnovu morfologije i funkcije, definiravši ih kao poremećaje u kojima je miokard strukturno i funkcijski abnormalan, u odsustvu koronarne bolesti srca, arterijske hipertenzije, valvulnih ili prirođenih bolesti ili njihova prisutnost ne objašnjava izraženu disfunkciju miokarda. Europska klasifikacija u osnovi dakle ima kardijalni fenotip i znatno se razlikuje od američke. Kardiomiopatije u sklopu neuromuskularnih poremećaja uvrštene su tako u jedan od morfoloških oblika.[10] Poznavanje molekulske razine bolesti ne može u potpunosti nadomjestiti kliničku klasifikaciju jer različite mutacije unutar istog gena mogu biti uzrok različitih poremećaja (npr. mutacije koje zahvaćaju susjedne aminokiseline u teškom lancu beta miozina mogu biti uzrok hipertrofijske ili dilatacijske kardiomiopatije).

Hipertrofijska kardiomiopatija (HCM): bolest je sarkomere, nasljeđuje se autosomno dominantno, a karakterizirana je neobjašnjivom hipertrofijom lijeve (ponekad i desne) klijetke, često s najjačim zahvaćanjem interventrikulskog septuma, mišićnom disorganizacijom i fibrozom. HCM je je najčešća nasljedna bolest miokarda s prevalencijom oko 0,2%, vrlo je heterogene prirode i tijeka. Konvencionalni ehokardiografski kriterij za dijagnozu HCM je debljina stijenke LV ≥1,5 cm, u odsustvu tlačnog opterećenja. Do sada je utvrđeno oko 400 mutacija devet gena odgovornih za sintezu proteina sarkomere koje uzrokuju HCM. Te mutacije uglavnom povećavaju aktivaciju miofilamenata i time kontraktilnost mio-

However, in 2008 the European Society of Cardiology divided cardiomyopathies according to morphology and function, defining them as disorders where the myocardium is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular or congenital heart diseases or their presence does not explain the pronounced myocardial dysfunction. The European classification is based on cardiac phenotype and greatly differs from the American one. Cardiomyopathies as a part of neuromuscular disorders are so listed as one of the morphological types.[10] Knowledge of molecular level of the disease can not fully compensate for the clinical classification, because different mutations within the same gene can cause different disorders (e.g. mutations affecting adjacent amino acids in the beta myosin heavy chain may be a cause of hypertrophic or dilated cardiomyopathy).

Hypertrophic cardiomyopathy (HCM): disease of sarcomere, with autosomal dominant inheritance, is characterized by unexplained hypertrophy of the left (sometimes right) ventricle, often predominately affecting interventricular septum, muscular disorganization and fibrosis. HCM is the most common inherited myocardial disease with prevalence of around 0.2%, it is of very heterogeneous nature and progress. Conventional echocardiographic criterion for the diagnosis of HCM is LV wall thickness ≥1.5 cm, in the absence of pressure load. Around 400 mutations of the nine genes responsible for the synthesis of sarcomere proteins causing HCM have been determined so far. These mutations mainly

cita dovodeći do prekomjerne potrošnje energije. Ostalih 7 gena odgovorno je pojedinačno za oko 1-5% slučajeva bolesti. Relaksacija LV (proces koji troši puno energije) se međutim u bolesnika s HCM paradoksno usporava. U miševa s mutacijom teškog lanca miozina dokazano je da diltiazem, inhibitor kalcijevih L-kanalića, spriječava disregulaciju kalcija u sarkoplzamatskom retikulumu i stoga nastanak hipertrofije miokarda. U tijeku je studija ispitivanja primjene diltiazema u bolesnika s pretkliničkom hipertrofijom.[2,9-13,15]

Glavno patofiziološko obilježje bolesti je dijastolička disfunkcija uzrokovana poremećenom relaksacijom i rastezljivošću LV. Druge bitne karakteristike su razvoj opstrukcije (gradijenta tlaka) u izlaznom ili središnjem dijelu LV, mitralna regurgitacija, ishemija miokarda i aritmije. Većina bolesnika je asimptomatska i dijagnoza se često postavi slučajno snimanjem EKG. Tipični simptomi su zaduha,(90%) angina (70-80%) i/ili sinkope (20% bolesnika). EKG je patološki promjenjen u oko 95% bolesnika. Prirodni tijek bolesti je također vrlo različit; iznenadna smrt obično se javlja u bolesnika bez ili s malo simptoma, uglavnom u mladih odraslih osoba, a mehanizam smrti je najčešće pojava ventrikulske tahikardije, odnosno fibrilacije.[2,9,11-14]

Simptomi uzrokovani opstrukcijom izlaznog trakta LV koji se nalazi u oko 30% bolesnika mogu se ublažiti lijekovima ili intervencijama. Mogućnosti liječenja bolesnika bez opstrukcije su znatno manje, ali u zadnje vrijeme ima izvjesnih rezultata s primjenom modulatora energije (trimetazidin, perhexilin).[12]

Dilatacijska kardiomiopatija (DCM): je progresivna, obično ireverzibilna bolest i najčešći razlog transplantacije srca. Prevalencija bolesti je oko 1/2500, a incidencija oko 2,5/100.000 stanovnika godišnje. Glavna obilježja bolesti su dilatacija ventrikula, sistolička disfunkcija, smrt kardiomiocita i fibroza. Dijagnoza se postavlja na temelju anamneze, kliničkog nalaza te tipičnog ehokardiografskog ili nalaza magnetske rezonancije koji pokazuju stanjenje stijenke u odnosu na dimenzije šupljina. Dilatacija desnog ventrikula može biti izražena, ali nije potrebna za postavljanje dijagnoze. Bolest klinički može postati manifestna u svim dobnim skupinama, ali najčešće u 3. ili 5. dekadi života. U odraslih bolest je češća u muškaraca. Desetogodišnje preživljavanje iznosi oko 50%. Primarna DCM uzrokovana je genetskim, miješanim (uglavnom nenasljednim), i stečenim uzrocima. Mnogi uzroci sekundarne DCM su sustavne prirode (***Tablica 1***).[2, 7,11,16-18]

Bolest je nasljedna u oko trećine do polovice bolesnika, najčešće se nasljeđuje autosomno dominantno, i krajnji je fenotip različitih mutacija raznolikih komponenti strukture i funkcije kardiomiocita. Iako su mutacije vrlo različite, sve dovode do oštećenja kontraktilne sposobnosti kardiomiocita. Do sada je otkriveno više od 40 oboljelih gena. Autosomno dominantni oblici bolesti primarno su uzrokovani mutacijama gena odgovornih za sintezu proteina citoskeleta. Bolest, iako rjeđe uzrokuju i mutacije gena odgovornih za sintezu proteina sarkomere, jezgrine membrane, interkaliranih diskova i metabolizma kalcija. Oboljeli geni odgovorni za sintezu kontraktilnih proteina, dovode do suprotnih funkcijskih promjena nego isti geni u HCM. Promjene strukture i funkcije kardiomiocita podstiču autofagiju i apoptozu.[11]

U razvijenim zemljama jedan od najvažniji uzroka ove bolesti u odraslih predstavlja kronična konzumacija alkohola. Dijagnoza alkoholne kardiomiopatije postavlja se isključivanjem drugih uzroka, a stupanj bolesti ovisi o prosječnom dnevnom unosu alkohola i trajanju abususa. U mnogih bolesnika liječenih antraciklinima (doxorubicin, daunorubicin)

increase the activation myofilamenats and myocyte contractility thus leading to excessive energy consumption. The remaining 7 genes are individually responsible for about 1-5% of cases of the disease. The relaxation of the LV (the process that consumes a lot of energy) is, however, in patients with HCM paradoxically slowed down. In mice with myosin heavy chain mutation, it has been proven that diltiazem, an inhibitor of L-type calcium channels, prevents dysregulation of calcium in sarcoplasamatic reticulum and thus the occurrence of myocardial hypertrophy. The study examining the use of diltiazem in patients with preclinical hypertrophy is underway.[2,9-13,15]

The main pathophysiological feature of the disease is diastolic dysfunction caused by impaired relaxation and LV compliance. Other important features are the development of obstruction (pressure gradient) in the outflow or mid part of the LV, mitral regurgitation, myocardial ischemia and arrhythmias. Most of the patients are asymptomatic and diagnosis is often made accidentally at the time of ECG recording. Typical symptoms are dyspnea (90%), angina (70-80%) and or syncope (20% of patients). ECG is pathological in approximately 95% of patients. The natural course of the disease is also very different; sudden death usually occurs in patients with no or few symptoms, mostly in young adults, while a mechanism of death is mostly ventricular tachycardia or fibrillation.[2,9,11-14]

The symptoms caused by the LV outflow tract obstruction occurring in about 30% of patients can be alleviated by medications or interventions. Treatment options for patients without obstruction are much smaller, but recently certain results have been achieved by using energy modulators (trimetazine, perhexiline).[12]

Dilated cardiomyopathy (DCM): is a progressive, usually irreversible disease and the most common reason for heart transplantation. The prevalence of the disease is about 1/2500, and the incidence of around 2.5/100 000 inhabitants per year. The main features of the disease are ventricular dilatation, systolic dysfunction, cardiomyocyte death and fibrosis. Diagnosis is made based on anamnesis, clinical findings and typical echocardiographic or magnetic resonance findings showing wall thinning compared to the dimensions of the cavities. The dilatation of the right ventricle can be pronounced, but it is not required for making diagnosis. The disease can become clinically manifested in all age groups, but usually in the 3rd or the 5th decade of life. In adults, the disease is more common in men. Ten-year survival is around 50%. The primary DCM is caused by genetic, mixed (mostly nonhereditary), and acquired causes. Many causes of secondary DCM are of systemic nature (***Table 1***).[2,7,11,16-18]

The disease is in about one third to a half of patients. It is most commonly hereditary autosomal dominant disease, while the ultimate phenotype shows different mutations of various structural components and cardiomyocyte functions. Although mutations are very different, all of them cause damage to contractile ability of cardiomyocytes. There have been more than 40 disease genes discovered so far. Autosomal dominant types of the disease are primarily caused by mutations of genes responsible for cytoskeletal protein synthesis. The disease is, although more rarely, caused by the gene mutations responsible for the synthesis of sarcomere proteins, nuclear membrane, intercalated discs and calcium matabolism. Disease genes responsible for the synthesis of contractile proteins lead to adverse functional changes unlike the same genes in HCM. Changes in the structure and function of cardiomyocytes stimulate autophagy and apoptosis.[11]

kardiomiopatija se obično razvija postupno i podmuklo. Patogenetsku ulogu imaju reaktivni kisikovi radikali i oštećenje mitohondrija. Primjena dexrazoxana može biti kardioprotektivna jer dovodi do smanjenog stvaranja slobodnih radikala. Bolest se može rano otkriti neinvazivnim obradom, poglavito ehokardiografiom te biokemijskim pretragama, ali mnogi problemi ostaju i dalje neriješeni.

Općenito u nastanku DCM vrlo važnu ulogu ima imunološki sustav. Dijagnoza virusnih i ostalih uzroka zasniva se na dobro utvrđenim histološkim, imunološkim i imunohistokemijskim kriterijima analize uzoraka miokarda dobivenih biopsijom. Autoimuni kronični miokarditis karakterizira prisustvo autoantitijela na kardijalni miozin, muskarinske kolinergične receptore, mitohiondrijske proteine, aktin, tubulin, troponin i još neke druge. Genetski mehanizmi koji dovode do autoimunog miokarditisa uglavnom su nepoznati. Mehanizmi nastanka DCM prikazani su u ***Tablici 2***.[2,11,15-17]

In developed countries, one of the most important causes of this disease in adults is chronic alcohol consumption. The diagnosis of alcoholic cardiomyopathy is made by excluding other causes, while the degree of the disease depends on an average daily intake of alcohol and duration of abusus. In many patients treated with anthracyclines (doxorubicin, daunorubicin), cardiomyopathy usually develops slowly and insidiously. Reactive oxygen radicals and damage to mitochondria have a pathogenetic role. The use of dexrazoxane may have cardioprotective effect, because it leads to decreased production of free radicals. The disease can be early detected by non-invasive workup, especially by echocardiography and biochemical tests, but many problems still remain unsolved.

Generally, in occurrence of DCM, the immune system plays a very important role. The diagnosis of viral and other causes is based on the well-established histological, immunological and immunohistochemical criteria of analysis of myocardial samples obtained by biopsy. Autoimmune chronic myocarditis is characterized by the presence of autoantibodies to cardiac myosin, muscarinic cholinergic receptors, mitochondrial proteins, actin, tubulin, troponin, and some other. Genetic mechanisms that lead to autoimmune myocarditis are usually unknown. Mechanisms of development of DCM are shown in ***Table 2***.[2,11,15-17]

Table 2. *Mechanisms responsible for dilated cardiomyopathy.*

Disturbed cytoskeletal — sarcomeric link: • Genetic mutation (sarcolemma-sarcomere gene) • Viral infection (coxsackie virus myocarditis) • Non-viral infection (Chagas disease) • Toxicity (adriamycin and alcohol)
Apoptosis
Autoantibodies and autoimmune disease
Metabolic disturbance storage disease
Mitochondrial dysfunction
Ion-channel disruption
Chronic incessant tachyarrhythmias
Peripartum
Infiltrative disease
Endomyocardial disease
Endocrinopathies
Nutritional deficiencies
Electrolyte disturbance

Modified from: Jefferies JL, Towbin JA. Lancet. 2010;752-62.

Liječenje DCM usmjereno je uglavnom na liječenje ZS i sprečavanje razvoja komplikacija odnosno progresije bolesti. Molekularna složenost DCM ukazuje na ograničenu mogućnost specifičnog modificirajućeg liječenja. Možda je potreban širji pristup te primjena regenerativnog liječenja. Ako je moguće treba utvrditi točni uzrok bolesti kako bi se i liječenje moglo što točnije odrediti. Temeljna ostaje inhibicija renin-angiotenzin-aldosteronskog sustava i simpatičkog sustava s ili bez primjene diuretika, ovisno o stupnju bolesti. Smanjenje tlačnog opterećenja može se postići primjenom nitroglicerina, nitroprusida ili neseretida. U bolesnika s izraženim ZS, hipotenzijom, hipoperfuzijom i povišenim tlakovima punjenja, potrebna je i. v. primjena inotropa odnosno

The treatment of DCM is mainly focused on the treatment of HF and prevention of the development of complications or disease progression. Molecular complexity of DCM indicates the limited ability of a specific modifying treatment. A broader approach and the use of regenerative treatment may be necessary. If it is possible, a correct cause of the disease should be determined in order to determine a treatment as precisely as possible. The inhibition of the renin-angiotensin-aldosterone system and sympathetic system with or without the use of diuretics, depending on a stage of the disease, still remains the basic option. Reduction of the pressure load can be achieved by using nitroglycerin, nitroprusside, or neseritide. In patients with pronounced HF, hy-

vazopresora. Bolesnicima s istisnom frakcijom manjom od 30% i znacima ZS usprkos optimalnog medikamentnog liječenja indicirana je ugradnja kardioverter defibrilatora. Resinkronizacijska terapija poboljšava koordinaciju i relaksaciju stijenki klijetki dovodeći do izvjesnog stupnja reverzne remodelacije i poboljšanja preživljavanja u oko 2/3 bolesnika. Kirurško liječenje DCM s kongestivnim ZS jedno je od najbrže razvijajućih područja kardiovaskularne kirurgije s ciljem poboljšanja biofizike LV i smanjenja nepovoljne remodelacije. Transplantacija srca indicirana je u najtežih bolesnika tj. onih koji trebaju inotropnu ili mehaničku potporu. Primjena mehaničke podrške cirkulaciji značajno je poboljšala preživljavanje bolesnika s terminalnim stupnjem DCM koji čekaju transplantaciju, ali i onih u kojih transplantacija nije moguća. Razina N-terminalnog distrofina smanjena je u srcima bolesnika sa svim oblicima DCM, a smanjenje mehaničkog stresa primjenom podrške cirkulaciji dovodi do reverzne remodelacije distrofina i samog srca.[11,17]

U načinu liječenja miokarditisa i dalje postoje nesuglasice. Kombinacija kortikosteroida i azatioprina bila je učinkovita u bolesnika s imunim mehanizmom dokazanim na uzorcima miokarda dobivenim biopsijom te u miokarditisu orijaških stanica. Tijekom zadnjih 10 godina jako je porastao interes za liječenje ZS matičnim stanicama, ali neka su istraživanja pokazala da taj pristup dovodi samo do parakrinog porasta razine faktora rasta, bez stvaranja novog miokarda.[11,15-17]

Spužvasta kardiomiopatija ili nekompaktni lijevi ventrikul udružena je sa širokim spektrom kliničkih i patofizioloških nalaza, a prirodni tijek i prognoza izgleda bolji su nego se ranije smatralo. Odrasli bolesnici sa sporadičnom ili nasljednom bolešću imaju relativno dobru prognozu, a oni koji imaju ZS, epizode ventrikulske tahikardije ili proširenu lijevu pretklijetku imaju nestabilni tijek i lošiju prognozu.[11,15-17]

Peripartalna kardiomiopatija je relativno rijetki, idiopatski oblik DCM, koji se javlja u žena za vrijeme zadnjeg mjeseca trudnoće ili prvih mjeseci nakon porođaja, a dijagnoza se postavlja isključivanjem drugih uzroka ZS. Lijeva klijetka ne mora biti dilatirana, ali je istisna frakcija uvijek <45%. Etiologija bolesti je nepoznata, a mogući patofiziološki mehanizmi su: akutni miokarditis, abnormalni imuni odgovor u trudnoći (ulazak fetalnih hematopoetskih stanica u majčinu cirkulaciju), abnormalna reakcija na hemodinamski stres uzrokovan trudnoćom i prekomjerno stvaranje prolaktina. Oksidativni stres dovodi do aktivacije katepsina D (proteaza) koji cijepa prolaktin u njegov antiangiogeni i proapoptotički fragment (16kDa prolaktin) koji inhibira proliferaciju i migraciju endotelnih stanica, podstiče njihovu apoptozu, dovodi do oštećenja kapilara, izaziva upalu, vazokonstrikciju i disfunkciju kardiomiocita. Dijagnoza ostaje izazov jer simptomi često sliče uobičajenim smetnjama koje žene mogu imati za trudnoće. Prirodni tijek bolesti varira od potpunog oporavka do teške dekompenzacije i moguće smrti. U epidemiološkim studijama dokazani su sljedeći rizični čimbenici: više porođaja, blizanačke trudnoće, starija ili mlađa dob, produžena tokoliza, preeklampsija, gojaznost i genetska predispozicija. Moguće je da se pod hemodinamskim stresom trudnoće bolest razvija u žena koje imaju prikriveni oblik obiteljske DCM.[2,19]

Liječenje je slično liječenju bolesnika sa sistoličkom disfunkcijom druge etiologije. Do normalizacije funkcije LV dolazi u oko 23-54% bolesnica, a smrtnost iznosi 11,4-30%. Dokazano je smanjenje mortaliteta bolesnica koje su liječene bromkriptinom u usporedbi s placebom. Najviši rizik ponovnog razvoja bolesti imaju žene koje ponovno zatrudne, a čija je istisna frakcija iznosila <25%. Daljnja istraživanja i napre-

potension, hypoperfusion and elevated filling pressures, the IV application of inotropes or vasopressors is required. Patients with ejection fraction less than 30% and signs of HF despite optimal medicamentous treatment undergo implantation of cardioverter defibrillator. Resynchronization therapy improves the coordination and relaxation of the ventricular walls leading to a certain degree of reverse remodeling and improvement of survival in about 2/3 of patients. Surgical treatment of DCM with congestive HF is one of the fastest developing areas of cardiovascular surgery aimed at improvement of LV biophysics and reduction of adverse remodeling. Heart transplantation is indicated in the most seriously ill patients or those who need inotropic or mechanical support. The application of mechanical support to circulation has significantly improved the survival of patients with end-stage DCM who are awaiting the transplantation, but also those in whom the transplantation is not possible. The level of N-terminal dystrophin is reduced in the hearts of patients with all forms of DCM, while the reduction of mechanical stress by using circulatory support leads to reverse remodeling of dystrophin and the heart itself.[11,17]

There are still disagreements as to the method of treating myocarditis. The combination of corticosteroids and azathioprine was effective in patients with immune mechanism proven in myocardial samples obtained by biopsy, and in the giant cells myocarditis. During the last 10 years, there is an increasing interest in the treatment of heart failure by stem cells, but some researches have shown that this approach only leads to paracrinal increase in the level of growth factors, without creating a new myocardium.[11,15-17]

Spongyform cardiomyopathy or a left ventricular noncompaction is associated with a wide spectrum of clinical and pathophysiological findings, while a natural course and prognosis seem to be better than what was previously thought. Adult patients with sporadic or hereditary disease have a relatively good prognosis, while those who have HF, episodes of ventricular tachycardia or enlarged left atrium have an unstable course and worse prognosis.[11,15-17]

Peripatum cardiomyopathy is a relatively rare idiopathic form of DCM, which occurs in women during the last month of pregnancy or the first months after delivery, while the diagnosis is made by excluding some other causes of HF. The LV may not be dilated, but the ejection fraction is always <45%. The etiology of the disease is unknown, while possible pathophysiological mechanisms are: acute myocarditis, abnormal immune response during pregnancy (entry of fetal hematopoietic cells into the maternal circulation), abnormal response to hemodynamic stress caused by pregnancy and excessive production of prolactin. Oxidative stress leads to activation of cathepsin D (protease) that cleaves prolactin to its antiangiogenic and proapoptotic fragment (16kDa prolactin), which inhibits proliferation and migration of endothelial cells, stimulates their apoptosis, causes damage to the capillaries, causes inflammation, vasoconstriction and cardiomyocyte dysfunction. Making a diagnosis remains a challenge, because the symptoms often resemble to the usual difficulties that women may have during pregnancy. The natural course of the disease varies from complete recovery to severe decompensation and potential death. In epidemiological studies, the following risk factors have been proven: multiple deliveries, twin deliveries, older or younger age, prolonged tocolysis, preeclampsia, obesity, and genetic predisposition. It is possible that under the hemodynamic stress of pregnancy, the disease develops in women who have hidden form of familial DCM.[2,19]

dak u liječenju bili bi značajno poboljšani osnivanjem nacionalnih i internacionalnih registara bolesti.[2,19]

Aritmogena kardiomiopatija desne klijetke (AKDV) nasljedna je bolest dezmosoma, s nadomještajem miokarda fibroznim i/ili masnim tkivom u desnom, ali i lijevom ventrikulu, što dovodi do aritmija, glavnog kliničkog obilježja bolesti. Tijekom zadnjih nekoliko godina je posebice primjenom genetskih analiza postignut veliki napredak u dijagnostici i razjašnjenju njene etiologije. Mutacije pet gena odgovornih za sintezu dezmosomalnih proteina (desmoplakin, plakoglobin, plakofilin 2, desmoglein 2, desmokolin 2) otkrivene su u bolesnika s AKDV kao i gena za faktor rasta beta3 i za transmembranski protein 43. Redistribucija plakoglobina je glavna karakteristika AKDV i može služiti kao dijagnostički test u uzorcima endomiokarda. Adipogeni transkripcijski faktor kao što je PPARG (peroksisomalni proliferacijski aktivirani receptor gama) može također utjecati na promjenu unutarstaničnog metabolizma lipida i doprinositi fibroznoj i masnoj infiltraciji.[11,20]

Dijagnoza AKDV temelji na dokazu strukturnih, funkcijskih i elektrofizioloških abnormalnosti koje odražavaju osnovne histološke promjene. Tehnički napredak NMR i ehokardiografije, omogućili su dobar prikaz desne klijetke i procjenu težine bolesti. Smetnje repolarizacije su rani i senzitivan znak razvoja bolesti. Inverzija T vala u odvodima V1, V2 i V3 normalno se susreće u zdravih osoba, starijih od 14 godina, u svega oko 4% žena i 1% muškaraca pa su te promjene dosta specifične i smatraju se glavnim dijagnostičkim pokazateljima AKDV. Zakašnjela depolarizacija u desnim prekordijalnim odvodima također je česta. Novi veliki i mali dijagnostički kriteriji AKDV objavljeni su 2010 god. Današnje liječenje terminalnog stadija AKDV uključuje konvencionalnu terapiju ZS, ali rezultati genetskih istraživanja ukazuju da bi se ciljno liječenje moglo sastojati u restituciji signalnih puteva i modifikaciji metabolizma lipida djelovanjem na PPAR.[11,20]

Restrikcijska kardiomiopatija (RCM): može biti idiopatska (primarna) ili je miokard zahvaćen sistemskim poremećajem (u odsustvu ishemijske, hipertenzivne, valvulne ili prirođene srčane bolesti), a karakterizirana je smetnjama punjenja, normalnim ili smanjenim volumenima lijeve i desne klijetke i u pravilu normalnom sistoličkom funkcijom. Primarna RCM je vrlo rijetka, a može biti uzrokovana mutacijama istih gena (odgovornih za sintezu proteina sarkomere) kao i HCM ili DCM. RCM je u većini slučajeva sekundarna, može biti infiltracijska ili neinfiltracijska i javlja se s ili bez obliteracije klijetki. Infiltracija može biti intersticijska (amiloidoza, sarkoidoza) ili stanična (hemokromatoza). Neovisno o etiologiji klijetke su u pravilu male (općenito <110 mL/m^2), krute, s posljedičnim otežanim punjenjem. Dijastolički tlak u klijetkama, tlakovi u pretklijetkama kao i plućni kapilarni tlak mogu biti izrazito povišeni, a zbog nedovoljnog punjenja klijetki dolazi do smanjenja minutnog volumena. Fibrilacija atrija česta je u idiopatskom obliku bolesti i u amiloidozi. Karakterističan je izrazito povišen jugularni venski puls s izraženim valovima x i y. Osim ehodoplerkardiografije u utvrđivanju etiologije bolesti važnu ulogu ima magnetska rezonancija. Vrlo je bitno razlikovati RCM od konstrikcijskog perikarditisa što i dalje koji puta ostaje pravi izazov. Biopsija endomiokarda može biti korisna u bolesnika s izraženim konstrikcijsko-restrikcijskom obilježjima zbog mogućnosti ostavljanja specifične dijagnoze histološkom analizom. Liječenje RCM je empirijsko i usmjereno uglavnom na liječenje dijastoličke disfunkcije, koje je još uvijek nezadovoljavajuće. Smanjenje povišenih dijastoličkih tlakova u klijetkama primjenom diuretika do-

The treatment is similar to the treatment of patients with systolic dysfunction of some other etiology. Normalization of the LV function occurs in approximately 23-54% of patients, while mortality ranges from 11.4 to 30%. Reduction of mortality of patients treated by bromcriptine compared to placebo has been proven. Women who become pregnant again, ejection fraction was <25% exposed to the highest risk of redevelopment of the disease. Further researches and progress in treatment were significantly improved by establishing national and international registries of disease.[2,19]

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary disease of desmosomes, with the replacement of the myocardium by fibrous and/or fatty tissue not only in the right, but also in the left ventricle, causing arrhythmias, which is the main clinical feature of the disease. During the last few years, a great progress has been achieved in diagnostics and explanation of its etiology especially by applying genetic analyses. Mutations of five genes responsible for synthesis of desmosomal proteins (desmoplakin, plakoglobin, plakofilin 2, desmoglein 2, desmocollin 2) were detected in patients with ARVC as well as genes for growth factor beta3 and for transmembrane protein 43. The redistribution of plakoglobin is the main characteristic of ARVC and can be used as a diagnostic test in endomyocardial samples. Adipogenic transcription factor such as PPARG (peroxisome proliferator-activated receptor gamma) can also influence the intracellular lipid metabolism and contribute to the fibrous and fatty infiltration.[11,20]

The diagnosis ARVC is based on evidence of structural, functional and electrophysiological abnormalities that reflect the basic histological changes. The technical progress of NMR and echocardiography has provided a good image of the right ventricle and assessment of the severity of the disease. Repolarization disorders are an early and sensitive sign of the development of the disease. Inversion of the T wave in the leads V1, V2 and V3 are normally encountered in healthy persons older than 14 years, in only about 4% of women and 1% of men, so such changes are quite specific and are considered the main diagnostic indicators of ARVC. Delayed depolarization in the right precordial leads is also common. New large and small ARVC diagnostic criteria were published in 2010. The today's treatment of ARVC endstage includes conventional therapy of heart failure, but the results of genetic researches indicate that the target treatment could consist of restitution of signaling pathways and the modification of lipid metabolism by exerting effect on PPAR.[11,20]

Restrictive cardiomyopathy (RCM): can be idiopathic (primary) or the myocardium is affected by systemic disorder (in the absence of ischemic, hypertensive, valvular or congenital heart disease), and is characterized by the filling disorders, normal or decreased volumes of the left and right ventricle and principally normal systolic function. The primary RCM is very rare and it can be caused by mutations of these genes (responsible for the synthesis of sarcomere proteins) as well as HCM or DCM. RCM is in most cases the secondary, but it can be infiltrative or non-infiltrative disorder and occurs with or without obliteration of the ventricles. Infiltration may be interstitial (amyloidosis, sarcoidosis) or cellular (hemochromatosis). Regardless of the etiology, ventricles are principally small (generally <110 ml/m^2), rigid, with a consequential restrictive filling. Diastolic pressure in ventricles, pressures in the atrium and the pulmonary capillary pressure may be highly elevated, while insufficient filling of the ventricles causes lower minute volume. Atrial fibrillation is common in the idiopathic form of the disease and amyloi-

vodi do izvjesnog poboljšanja sistemske i plućne kongestije, ali je potreban oprez kako ne bi došlo do prevelikog smanjenja venskog priljeva. Održavanje sinusnog ritma je vrlo bitno jer fibrilacija atrija koja je česta u tih bolesnika još više pogoršava punjenje klijetki. Beta-blokatori su korisni u ranoj fazi bolesti, ali kasnije mogu pogoršati simptome. Zbog velike učestalosti tromboembolijskih komplikacija, u većine bolesnika je, bez razlike na ritam, indicirana antikoagulantna terapija.[21] Klasifikacija restrikcijskih kardiomiopatija prikaza je u ***Tablici 3***.

dosis. Highly elevated jugular venous pulse with pronounced x and y waves is characteristic. Besides echodopplercardiography, magnetic resonance plays an important role in determining the etiology of the disease. It is very important to distinguish RCM from constrictive pericarditis which still sometimes remains a challenge. Endomyocardial biopsy may be useful in patients with pronounced constrictive-restrictive characteristics due to a possibility of making a specific diagnosis by using histological analysis. The treatment of RCM is the empirical treatment mainly focusing on the treatment of diastolic dysfunction, which is still unsatisfactory. Lowering of elevated diastolic pressures in the ventricles by using diuretics leads to certain improvement of systemic and pulmonary congestion, but caution is to be taken as to avoid excessive lowering of the venous flow. Maintenance of sinus rhythm is very important, because atrial fibrillation, which is common in these patients exacerbates the filling of the ventricles. β-blockers are useful in early stages of the disease, but later may worsen the symptoms. Due to the high incidence of thromboembolic complications, anticoagulant therapy is indicated in most patients, regardless of rhythm.[21] The classification of restrictive cardiomyopathies is shown in ***Table 3***.

Table 3.
Classification of the restrictive cardiomyopathies.

Myocardial
Non-infiltrative cardiomyopathies
Idiopathic
Familial
Pseudoxanthoma elasticum
Scleroderma
Infiltrative cardiomyopathies
Amyloidosis
Sarcoidosis
Storage disease
Hemochromatosis
Gaucher disease
Fabry disease
Glycogen storage diseases
Endomyocardial
Obliterative
Endomyocardial fibrosis
Hypereosinophilic syndrome
Nonobliterative
Carcinoid
Malignant infiltration
Iatrogenic (radiation, drugs)

Modified from: Hoit BD. In Fuster V, Walsh RA, Harrington RA, editors. Hurst's the Heart, 13th ed. McGraw Hill: 2011; 865.

Rasprava

Sve dosadašnje klasifikacije kardiomiopatija su na neki način kontradiktorne i zapravo se ni jedna od predloženih ne može smatrati idealnom. Klasifikacija Američkog kardiološkog društva uzela je u obzir dostignuća molekulske genetike ali ne daje strategiju za kliničku dijagnostiku, kao niti za način liječenja tj. više je znanstvena.[7,10]

Discussion

All previous classifications of cardiomyopathies are in a way contradictory and in fact, none of the proposed classifications can be considered an ideal classification. The classification by the American College of Cardiology took into account the achievements of molecular genetics, but it neither provides a strategy for clinical diagnostics nor for the treatment option, in other words, it is rather scientific.[7,10]

U općoj populaciji teško je raspoznati osobe s nasljednim kardiomiopatijama, a s malo simptoma ili znakova bolesti, stoga je i probiranje populacije neučinkovito. Mnogo korisnije je otkrivanje oboljelih unutar obitelji. Do sada nema čvrstog dokaza da bi jedna te ista mutacija sarkomere u nekih članova iste obitelji bila uzrok hipertrofijske, a u drugih dilatacijske kardiomiopatije. Nema preciznog odnosa između mutacije i njenih biofizičkih posljedica. Npr. apikalna se HCM uglavnom javlja u obiteljima ranije zahvaćenim opstrukcijskim oblikom bolesti. Nekompaktni LV mogu imati članovi obitelji s inače tipičnim oblicima HCM ili DCM. Usporedno s razvojem genomike otkrivaju se novi patogenetski mehanizmi i oblici kardiomiopatija, pa podjela na dilatacijsku, hipertrofijsku i restrikcijsku kardiomiopatiju postaje neodrživa i vjerojatno će se u budućnosti napustiti.[11,16]

Nove dijagnostičke metode su nužne i bez njih neće biti napretka u rasvjetljavanju etiologije i patogeneze bolesti. Treba odgovoriti da li je bitno smanjeno stvaranje energije ili promjena morfologije, što se prvo javlja i koji su procesi zajednički bez razlike na vrstu početnog oštećenja miokarda? Vrlo važno je međutim, da nove metode ne postanu same sebi svrhom, bez postignutog napretka u ciljnom liječenju bolesnika. Primjer je endomiokardna biopsija od koje se mnogo očekivalo, kako u dijagnostici tako i u iznalaženju načina liječenja na temelju patohistološkog nalaza, ali se s vremenom pokazalo da je njena korist ograničena. Utvrdimo li pomoću NMR da bolesnik ima edem miokarda, ostaje pitanje hoće li to promijeniti način njegova liječenja. Zadnjih 20 godina vrlo je mnogo učinjeno na unapređenju dijagnostike i etiologije kardiomiopatija, a znatno manje na kauzalnolm ili modificirajućem liječenju. Današnje liječenje bolesnika s kardiomiopatijama, posebice dilatacijskom previše je unificirano. Usprkos svim dostignućima DCM ostaje i dalje veliki izazov. Prognoza bolesti nije se značajnije promijenila tijekom zadnjih deset godina. Bitno je što ranije otkriti bolest i ne dozvoliti pogoršanje, bez razlike na etiologiju bolesti, tj. blokirati RAAS i simpatički sustav, smanjiti razinu citokina kao i odstraniti sve druge nepovoljne činioce. Možda čak i kauzalno liječenje neće poboljšati prognozu ako nismo istovremeno započeli i s blokadom aktiviranog RAAS. Tome u prilog govore primjeri poboljšanja morfologije i funkcije LV u bolesnika s hipertenzivnom, ali i s drugim oblicima kardiomiopatija. Određivanjem razine BNP ili NT-proBNP danas možemo, do izvjesne mjere, pratiti pogoršanje odnosno poboljšanje funkcije oštećenog miokarda.

Ostaju pitanja zašto se u nekih bolesnika uspije postići poboljšanje, a u drugih ne, koliko je bitna intervencija u asimptomatskoj fazi bolesti, koji su za to odgovorni činioci i što na molekulskom nivou određuje granicu oporavka? Uzročne mutacije dovode do malih staničnih promjene, koje dobro toleriraju svi nosioci tih mutacija tijekom izvjesnog razdoblja, a u mnogim slučajevima i tijekom čitavog života, što ukazuje da postoje brojni kompenzacijski mehanizmi. Prijelaz do manifestne bolesti može biti vrlo brz kako u HCM tako i u DCM sugerirajući postojanje kritične točke ("tipping point") na kojoj dolazi do dekompenzacije.[11,16]

In the general population, it is difficult to identify persons with hereditary cardiomyopathies with few symptoms or signs of the disease, therefore population screening is ineffective. Detection of patients within families is much useful. So far there has been no strong evidence that one and the same sarcomere mutation in some members of the same family could be the cause of hypertrophic and others dilated cardiomyopathy. There is no precise relationship between the mutation and its biophysical consequences. For example, apical HCM usually occurs in families previously affected by obstructive type of the disease. Family members with typical types of HCM or DCM may have left ventricular non-compaction. Parallel with the development of genomics, new pathogenetic mechanisms and types of cardiomyopathies are being discovered, so the division into dilated, hypertrophic and restrictive cardiomyopathy has become unsustainable and will probably be abandoned in the future.[11,16]

New diagnostic methods are necessary, and without them there will be no progress in clarifying the etiology and pathogenesis of the disease. The question should be answered is whether reduced production of energy or the change of morphology is essential, as well as which occurs first and what processes are the common regardless of the type of initial myocardial impairment? It is, however, very important that the new methods should not become an end in themselves, without any progress achieved in the target treatment of patients. An example is endomyocardial biopsy from which much was expected in both the diagnostics and in finding treatment options according to pathohistological findings, but eventually it was shown that its benefit was limited. If we determine that a patient has myocardial edema by using NMR, the question is whether it will change its treatment method. During the last 20 years very much has been done in respect of improvement of the diagnostics and etiology of cardiomyopathies and much less in respect of causal or modifying treatment. The present treatment of patients with cardiomyopathies, especially the dilated myopathies is too much unified. Despite all achievements, DCM remains a great challenge. Prognosis of the disease has not significantly changed during the last 10 years. It is important to detect the disease as early as possible and not to allow impairment, regardless of the etiology of the disease, that is, to block RAAS and the sympathetic system, reduce the level of cytokines and remove all other adverse factors. It may happen that even the causal treatment will not improve the prognosis, if we failed to start blockade of activated RAAS at the same time. This is supported by examples of improving the morphology and LV function not only in hypertensive patients, but also with other types of cardiomyopathies. Determination of BNP or NT-pro-BNP level enable us to today to monitor deterioration or improvement of myocardial function to certain extent.

The question remains why in some patients improvement can be achieved, while in others no improvement can be achieved, how essential the intervention in asymptomatic stage of the disease is, which factors are responsible for it, and what determines the limit of recovery at the molecular level? The causative mutations lead to slight cellular changes, which are well tolerable by all carriers of these mutations during a certain period of time, and in many cases even throughout whole life, showing that there are many compensatory mechanisms. The transition to manifest disease can be very fast both in HCM and DCM, suggesting the existence of tipping points when decompensation ocurrs.[11,16]

Novi načini liječenja trebali bi, barem malo, promijeniti stupanj staničnog oštećenja kako bi se održalo kompenzirano stanje. Identifikacija oboljelih gena pružila je nadu u nove načine i mogućnosti liječenja, ali je praksa pokazala da do toga zapravo rijetko dolazi. Međutim, za neke nasljedne kardiomiopatije rasvjetljavanje molekulske osnove, stvara mogućnost novog liječenja. HCM bi se trebala moći najlakše liječiti jer su specifični terapijski ciljevi otkriveni. AKDV također ima dovoljno specifičnosti da se može ciljano liječiti. Najteže će biti utjecati na multiple primarne defekte DCM. Izbjegavanje precipitirajućih činilaca okoline može biti vrlo bitno. Gensko-fenotipske korelacije mogu biti korisne jer će u nekim slučajevima poznavanje gena preusmjeriti način liječenja (npr. sklonost smetnjama kondukcije u bolesnika s DCM uzrokovanom mutacijom LMNA upućuje na potrebu ugradnje elektrostimulatora). Međutim, u većine kardiomiopatija korelacija između oboljelog gena i fenotipa danas je još uvijek od ograničene koristi u liječenju bolesnika.[11,12,15-17]

Zaključak

Kardiomiopatije će zbog svojih mnogo lica još jako dugo plijeniti našu pažnju i trebat će jako puno sati predanog rada da se iznađe što više točnih mehanizama bolesti i što je najvažnije, kauzalnih načina liječenja. Raznolikost kardiomiopatija posljedica je različitih genetskih, alelnih, epigenetskih i okolišnih činioca koji svi doprinose određenom fenotipu. Nasljedne kardiomiopatije su glavni uzrok srčanih bolesti u svim dobnim skupinama, često s početkom u adolescenciji, ili ranom odraslom životu. Ne samo bolesnici, nego i njihove obitelji obično su jako opterećeni spoznajom o prisustvu bolesti. Kao što je to i u drugim autosomno dominatnim poremećajima, nasljedne kardiomiopatije pokazuju značajnu fenotipsku raznolikost, čak unutar iste obitelji.

Koliko god napredovala genetika i razumijevanje patogeneze kardiomiopatija na molekulskom nivou, uvijek ćemo biti iznenađeni i zatečeni kliničkom slikom bolesti.

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*Address for correspondence: Klinički bolnički centar Sestre milosrdnice, Vinogradska cesta 29, HR-10000 Zagreb, Croatia.

Phone: +385-1-3787-111

E-mail: danijelplaninc@gmail.com

New treatment methods should change the degree of cellular impairment at least to a small extent in order to maintain the compensated condition. Owing to identification of genes affected by the disease, we look forward to some new treatment methods and options, but in practice this rarely happens. However, in regard to some hereditary cardiomyopathies, clarification of molecular basis leads to creation of a new treatment option. HCM should be the easiest disease to treat, because the specific therapeutic targets have been discovered. ARVC has also enough specific features for target treatment. Exerting impact on multiple primary defects of DCM will be the hardest thing to do. Avoiding precipitating environmental factors can be very important. Genetic and phenotypic correlations can be useful because in some cases, knowledge of genes will redirect the treatment method (e.g. tendency of conduction disorders in patients with DCM caused by mutations of LMNA indicates the need for implantation of a pacemaker). However, in most cardiomyopathies, correlation between the disease gene and phenotype still today shows limited benefits in the treatment of patients.[11-12, 15-17]

Conclusion

Cardiomyopathies will, due to its many faces, be attracting our attention for a long time and it will take a lot of hours of dedicated work to find as many precise mechanisms of the disease as possible, and most importantly, the causal treatment methods. The diversity of cardiomyopathies is the consequence of various genetic, allelic, epigenetic, and environmental factors, whereas all of them contribute to a particular phenotype. Hereditary cardiomyopathies are the main cause of cardiac diseases in all age groups, often beginning in adolescence age or early adult life. Not only patients, but also their families are usually heavily burdened with the knowledge of the presence of the diseases. As it is the case in other autosomal dominant disorders, hereditary cardiomyopathies show significant phenotypic diversity, even within the same family.

No matter to what extent genetics and understanding of pathogenesis of cardiomyopathies at a molecular level have advanced, we shall always be surprised and amazed by clinical manifestation of the disease.

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