

Stručni rad / Professional article

# Kardiomiopatija inducirana ventrikulskim ekstrasistolama

## *Ventricular extrasystole — induced cardiomyopathy*

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**SAŽETAK:** Ventrikulske ekstrasistole (VES) česta su i načelno benigna pojava, osobito ako se radi o bolesniku sa strukturno zdravim srcem. 1998. godine objavljena je prva studija u kojoj je dokazano da medikamentozna supresija ekstrasistolije rezultira oporavkom funkcije lijeve klijetke u dilatacijskoj kardiomiopatiji te je razvijen koncept VES inducirane kardiomiopatije (CMP). Sama pojavnost VES vrlo je velika u populaciji, raste s dobi, no točne podatke o incidenciji VES inducirane kardiomiopatije nemamo. Najvažniji čimbenik u razvoju ovog entiteta je “VES opterećenje”<sup>1</sup> no još se vode polemike oko točne definicije istog. Razvijeno je nekoliko životinjskih modela za rasvjetljavanje patofiziologije ove bolesti te se najvjerojatnije radi o funkcijskom poremećaju koji je u velikoj mjeri reverzibilan. U obradi ovih bolesnika potrebno je na sve dostupne načine detektirati sekundarne uzroke ekstrasistolije i kardiomiopatije, jer je VES inducirana CMP dijagnoza do koje dolazimo isključivanjem. Od terapijskih opcija na raspolaganju nam je medikamentozna terapija antiaritmicima te kateterska radiofrekventna (RF) ablacija. Randomizirane studije koje bi dale prednost jednoj od ovih opcija ne postoje. U posljednje vrijeme preferira se RF ablacija s vrlo dobrim rezultatima u reverziji kardiomiopatije i s malom učestalosti komplikacija. U ovom trenutku, VES inducirana CMP još je prilično prepoznata kao uzrok neishemijske kardiomiopatije.

**KLJUČNE RIJEČI:** ventrikulske ekstrasistole, kardiomiopatija, antiaritmici, radiofrekventna ablacija.

Ventrikulske ekstrasistole (VES) su jedna od najčešćih aritmija u radu kardiologa kliničara. Prije smatrane kao benigna pojava bez kliničkog značaja<sup>1</sup>, VES se sada povezuju s entitetom nazvanim VES inducirana kardiomiopatija. Svakodnevno raste količina dokaza koja povezuje ventrikulske ekstrasistole u inače strukturno zdravom srcu, s razvojem dilatacije lijeve klijetke (LV) i sniženjem vrijednosti ejeckijske frakcije (EF) LV<sup>2-4</sup>. Ovo stanje može se uspješno liječiti medikamentozno<sup>5</sup> ili kateterskom ablacijom, što rezultira normalizacijom dimenzija i funkcije LV<sup>6-8</sup>. Točna patofiziologija ove bolesti ostaje nerazjašnjena. Postoje neke spekulacije koje povezuju VES induciranu disinkroniju i

**SUMMARY:** Ventricular extrasystoles (PVC, Premature Ventricular Contraction) are a common and generally a benign phenomenon, especially in a patient with a structurally normal heart. The first study was published in 1998 which proved that medical suppression of extrasystole results in the recovery of the left ventricular function in dilatation cardiomyopathy, whereas the concept of PVC-induced cardiomyopathy (CMP) was developed. The incidence of PVCs itself is very large in population, rises with age, but we have no accurate data on the incidence of PVC-induced cardiomyopathy. The most important factor in the development of this disease is “PVC burden”, but the exact definition thereof is still being discussed. Several animal models have been developed for elucidating the pathophysiology of this disease and it is probably a functional disorder that is largely reversible. In the treatment of these patients it is necessary to detect secondary causes of extrasystole and cardiomyopathy in all available ways; because the PVC-induced CMP is diagnosis of exclusion. Out of therapeutic options we have antiarrhythmic drug therapy and catheter radiofrequency (RF) ablation at disposal. There are no randomized studies that would prefer one of these options. RF ablation, with very good results in the reversion of cardiomyopathy and with a low incidence of complications, has been preferred lately. At this point, PVC-induced CMP is still too seldom recognized as a cause of non-ischemic cardiomyopathy.

**KEYWORDS:** premature ventricular contraction, cardiomyopathy, antiarrhythmic drug therapy, catheter radiofrequency ablation.

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Ventricular extrasystoles (premature ventricular contraction, PVC) are one of the most common arrhythmia in the practice of cardiologic clinicians. Although it was considered to be a benign phenomenon without clinical significance<sup>1</sup>, PVC is now associated with the entity called the PVC-induced cardiomyopathy. The scope of evidence is growing on a daily basis linking the ventricular extrasystoles in the structurally normal heart to the development of left ventricular (LV) dilatation and the reduction in LV ejection fraction (EF)<sup>2-4</sup>. This condition can be successfully treated by drugs<sup>5</sup> or catheter ablation resulting in the normalization of the LV dimensions and functions<sup>6-8</sup>. The exact pathophysio-

VES induciranu kardiomiopatiju, slično kao kod već dobro poznatog negativnog utjecaja elektrostimulacije desne klijetke. Nadalje, promjene u ionskim kanalima i unutarstaničnom prometu kalcija predloženi su mehanizmi nastanka disfunkcije LV, slično kao što se događa u taži-kardiomiopatiji<sup>9</sup>. Do sada su razvijena dva modela za istraživanje ove bolesti koja su koristila pse mješance te je jasno pokazana povezanost između ekstrasistola i disfunkcije lijeve klijetke. Međutim, u ovim modelima nisu detektirane veće histopatološke promjene, tako da točni mehanizmi ove bolesti ostaju nepoznati<sup>10,11</sup>.

## Epidemiologija

Prevalencija VES ovisna je o dobi, tako da se nalazi u rasponu od <1% u djece pa do >60% u osoba starije životne dobi<sup>12</sup>. Čak do 75% ispitanika u standardnom snimanju holter elektrokardiograma (do 48 sati), imaju VES, dok u standardnom 12-kanalnom elektrokardiogramu učestalost iznosi samo 1%<sup>13</sup>. Dugo su se vremena VES u strukturno zdravom srcu smatrale kao sasvim benigna pojava, sve dok 1998. godine nije opisan povoljan učinak medikamentozne supresivne VES na dilatacijsku kardiomiopatiju te je razvijen koncept VES inducirane kardiomiopatije<sup>5</sup>. Točna prevalencija ove bolesti nije poznata, no sigurno je da ovaj entitet prema lo dijagnosticiran kao uzrok kardiomiopatije (CMP). Dominantno se javlja u osoba starije životne dobi, vjerojatno zbog činjenice da je potrebno mnogo vremena da učestale VES izazovu snižavanje funkcije LV<sup>14</sup>. Osim dužine trajanja VES, vrlo je važna i učestalost VES koja se mjeri udjelom (%) ili samim brojem tijekom 24 sata, takozvani "PVC burden" — VES opterećenje.

## Patofiziologija

VES inducirana kardiomiopatija ima neke sličnosti s drugim kliničkim entitetima kao što su taži-kardiomiopatija i kardiomiopatija inducirana desno-ventrikulskom elektrostimulacijom. Prije se smatralo da je ona u biti samo jedna podvrsta taži-kardiomiopatije, koja je dobro poznat fenomen u sklopu "brze" fibrilacije ili undulacije atrijske, drugih supraventrikulskih poremećaja ritma ili ventrikulske tahikardije. Ovaj patofiziološki mehanizam brzo je naišao na kritike jer su prosječne frekvencije kod VES inducirane CMP slične onima u sinusnom ritmu. Moguće je da učestale i usko vezane VES uzrokuju promjene u unutarstaničnom metabolizmu kalcija, transmembranskom prometu iona te na taj način iscrpljuju energetske zalihe miocita. Uz to, dolazi do promjena u hemodinamici te u dinamici srčanog pulsa uz vezane promjene u tonusu vaskulature<sup>15</sup>. Navedeni fenomen već je prije opisan kao postekstrasistolička potencijacija<sup>11</sup>. Sličnost sa CMP kod stimulacije desne klijetke (RV) očituje se ekscentričnom aktivacijom ventrikulskog miokarda uzrokovanog VES što dovodi do disinkronije. Kompenzatorne pauze nakon VES mijenjaju dinamiku punjenja i pražnjenja klijetke. Disinkronija rezultira s smanjenom globalnom efikasnošću klijetke, asimetričnom hipertrofijom stijenki, promjenama u perfuziji miokarda te na kraju povećanom potrošnjom kisika<sup>6</sup>.

Do sada su objavljena dva modela koja bi trebala rasvijetliti točne mehanizme ove bolesti, oba na psima mješancima. Akum i sur. su koristili dvokomorski elektrostimulator (obje elektrode u RV, jedna za "sensing", druga za stimulaciju) kojim su simulirali VES bigeminiju iz RV. Već nakon 4 tjedna došlo je do razvoja dilatacije LV i značajnog pada u sistoličkoj funkciji (EF sa 60% na 46%)<sup>10</sup>. Sličan model koristili

logy of this disease remains unclear. There are some speculations linking PVC-induced dyssynchrony to the PVC-induced cardiomyopathy, similar to the well-known negative effect of the right ventricular electrostimulation. Besides, changes in ion channels and intracellular transport of calcium are the proposed mechanisms of occurrence of the LV dysfunction, similar to what happens in case of tachycardiomyopathy<sup>9</sup>. Two models for studying this disease using mongrel dogs have been developed so far and the correlation between extrasystoles and the LV dysfunction has been clearly shown. However, no greater histopathological changes have been detected in these models, so that the exact mechanisms of these diseases remain unknown<sup>10,11</sup>.

## Epidemiology

The prevalence of PVC is age dependent, so that it ranges from <1% in children up to >60% in the elderly persons<sup>12</sup>. Up to 75% of subjects in standard Holter ECG recording (up to 48 hours) have PVC, while in standard 12-lead electrocardiogram the incidence is only 1%<sup>13</sup>. PVC had been long regarded as an entirely benign phenomenon in structurally normal heart until 1998 when the beneficial effect of PVC suppressive drugs on dilated cardiomyopathy was described and when the concept of PVC-induced cardiomyopathy was developed<sup>5</sup>. The exact prevalence of the disease is unknown, but it is certain that this entity is underdiagnosed as a cause of cardiomyopathy (CMP). It predominantly occurs in elderly people, probably due to the fact that it takes a long time for frequent PVCs to cause reduction of LV function<sup>14</sup>. In addition to the duration of PVCs, the incidence of PVC measured as the ratio (%) or the absolute number during 24 hours, the so-called "PVC burden" is very important.

## Pathophysiology

PVC-induced cardiomyopathy has some similarities to other clinical entities such as tachycardiomyopathy and cardiomyopathy induced by right ventricular electrostimulation. In the past, it was thought to be just one subtype of tachycardiomyopathy, which is a well-known phenomenon within the "fast" atrial fibrillation or undulation, other supraventricular arrhythmias or ventricular tachycardia. This pathophysiological mechanism soon faced criticism, because the average incidence in PVC-induced CMP is similar to that in sinus rhythm. It is possible that frequent and short-coupled PVCs cause changes in intracellular calcium metabolism and transmembrane ion transport thus depleting the energy supplies of myocytes. In addition, changes are made to the hemodynamics and heart rate dynamics with the associated changes in the vasculature tonus<sup>15</sup>. The above mentioned phenomenon has been previously described as a postextrasystolic potentiation<sup>11</sup>. The similarity to CMP in the right ventricular (RV) stimulation is reflected in eccentric activation of the ventricular myocardium caused by PVCs which leads to dyssynchrony. Compensatory pauses after PVC change the ventricular filling and discharging dynamics. Dyssynchrony results in reduced global efficiency of ventricles, asymmetric wall hypertrophy, changes in myocardial perfusion and ultimately in an increased consumption of oxygen<sup>6</sup>.

Two models that should elucidate the exact mechanisms of this disease have been published so far, both on mongrel dogs. Akum et al. used dual chamber pacemaker (the both electrodes in the RV, one for sensing, the other for stimulation) used for simulating PVC bigeminy from the RV. Only after four weeks LV dilatation developed followed by a significant decline in systolic function (EF from 60% to 46%)<sup>10</sup>. A similar model was used by Ellenbogen et al., where dila-

su Ellenbogen i sur. gdje je nakon 12 tjedana također došlo do dilatacije i značajnog pada u funkciji LV. Nadalje, već 2-4 tjedna nakon prestanka stimulacije došlo do oporavka funkcije LV. U tom radu napravljene su i histološke studije koje nisu našle znakova upale, fibroze, promjena u apoptozi ili u oksidativnoj fosforilaciji u mitohondrijima kod subjekata s CMP, što govori u prilog da je VES inducirana kardiomiopatija reverzibilno stanje bez većih patohistoloških i mitohondrijskih anomalija. Do promjene je došlo u efektivnom refrakternom periodu klijetke, što je znak električnog remodeliranja. Radi se dakle, dominantno o funkcijskoj, a ne strukturnoj abnormalnosti koja je uzrok CMP<sup>11</sup>. Činjenica da je kod psećeg modela, tako malo vremena bilo potrebno za razvoj CMP, baca sumnju na adekvatnost istog u slučaju interpolacije na ljude gdje je poznato da su potrebne godine za deterioraciju funkcije LV. Grupa autora iz Michigena razvila je ovčji model s vrlo sličnom metodologijom (dvokomorski elektrostimulator i inducirana VES bigeminija), no ovdje su se promjene u parametrima funkcije LV javile mnogo kasnije te su bile mnogo suptilnije. Na staničnoj razini, zabilježene su tek neke promjene u unutarstaničnom prometu kalcija koje bi mogle barem djelomično objasniti patofiziologiju ove bolesti (još neobjavljeni podaci).

### Karakteristike ventrikulskih ekstrasistola

Ne postoje strogo definirane granice učestalosti VES koje bi sigurno uzrokovale pad u funkciji LV. Neki bolesnici s vrlo visokim opterećenjem ne dobiju CMP, dok je drugi s mnogo manjim opterećenjem razviju, no to se ipak događa mnogo rjeđe. Sigurno je da i drugi parametri osim "VES opterećenja" igraju važnu ulogu u razvoju ove bolesti. Ipak, bolesnici sa sniženom EF imaju značajno više opterećenje od sličnih bolesnika s normalnom EF.

Različiti autori postavljaju drugačije granice kojima definiraju visoko opterećenje, 20.000/dan, >10.000/dan, >10% QRS, >10/sat, itd.<sup>6,16,17</sup>. Važno je za napomenuti da tek jedna trećina bolesnika s visokim VES opterećenjem razvije CMP. Pitanje je da li se radi o greški u metodologiji (uobičajeni 24 satni Holter) ili su odgovorni drugi, nepoznati momenti. Jedna studija pokazuje da granica od 24% VES dnevno ima zadovoljavajuću specifičnost (79%) i senzitivnost (78%) u razgraničavanju bolesnika s i bez CMP<sup>18</sup>. Velika većina idiopatskih VES proizlazi iz izlaznog trakta RV (oko 2/3), no značajan udio aritmijskih fokusa nalazi se u muskularnim tračcima iznad pulmonalne i aortne valvule (vidjeti članak dr. Anića u ovom broju časopisa<sup>18</sup>). Nešto su rjeđi fokusi u LV — slobodnoj stijenci, papilarnim mišićima ili fasciklima lijeve grane. Ventrikulska ektopija, dakako može biti i multifokalna što rezultira polimorfnim VES, no često su one iz izlaznog trakta dominantne. Zanimljivo je da je u jednoj studiji bila potrebna mnogo veća učestalost VES iz LV (>20%) naspram RV (>10%) za razvoj CMP što bi moglo govoriti u prilog VES inducirane disinkronije kao patofiziološkog mehanizma. Osim toga, VES širokog QRS-a (>150 ms) ili one epikardijalnog podrijetla nezavisan su prediktor razvoja CMP<sup>19</sup>.

Već prije smo napomenuli da je i trajanje ekstrasistolije važan prediktor razvoja CMP. Potrebne su godine, a ne samo mjeseci vrlo učestalih VES da bi došlo do razvoja CMP. Pacijenti bez ikakvih simptoma (kasnije se javljaju liječniku) ili oni s trajanjem palpitacija >60 mjeseci češće razvijaju kardiomiopatiju<sup>20</sup>. Pitanje utjecaja VES "coupling intervala" i VES interpolacije na razvoj CMP još nema jednoznačan odgovor.

tion and a significant decline in the LV function occurred after 12 weeks. Besides, already 2-4 weeks the cessation of stimulation was followed by the recovery of LV function. In this article, some histological studies were performed finding no signs of inflammation, fibrosis, changes in apoptosis or oxidative phosphorylation in mitochondria in subjects with cardiomyopathy, which confirms the thesis that PVC-induced cardiomyopathy is a reversible condition with no major pathohistological and mitochondrial anomalies. The change occurred in the effective refractory period of the ventricle, which is the sign of the electric remodelling. So, the most probably, it is predominantly the functional rather than structural abnormality that causes CMP<sup>11</sup>. The fact that in canine models it took so little time for CMP to develop, casts doubt on the appropriateness of the same in case of interpolation on people where we know that it takes years for the LV function to deteriorate. A group of authors from Michigan developed a sheep model with a very similar methodology (dual chamber pacemaker and induced PVC bigeminy), but here the changes in the parameters of LV function were detected much later and were much more subtle. At the cellular level, there were only a few changes in the intracellular transport of calcium which could at least partially explain the pathophysiology of this disease (still unpublished data).

### Characteristics of ventricular extrasystoles

There are no strictly defined limits of incidence of PVC, which would certainly cause a decline in LV function. Some patients with very high burden do not develop CMP, while the other with a much smaller burden develop it, however, it still happens a lot less often. It is certain that the other parameters except for "PVC burden" play an important role in the development of this disease. However, patients with lowered EF have significantly greater burden than similar patients with normal EF.

Various authors have set different boundaries which define high burden, 20,000/day, >10,000/day, >10% QRS, >10/hour, etc.<sup>6,16,17</sup>. It is important to note that only one third of patients with high PVC burden develop CMP. The question is whether an error in the methodology is concerned (the usual 24-hour Holter) or whether some other unknown moments are accountable. One study shows that the limit of 24% PVC a day is sufficiently specific (79%) and sensitive (78%) in dividing patients in those with and without CMP<sup>18</sup>. The vast majority of idiopathic PVC arises from the RV outflow tract (around 2/3), but a significant proportion of arrhythmic foci is positioned in the muscular extension above the pulmonary and aortic valve (see the article by Anić in this issue<sup>18</sup>). Foci in LV — the free wall, papillary muscles or fascicles of the left bundle branch are somewhat rarer. Ventricular ectopia, can of course be multifocal resulting in polymorphic PVC, but often those coming from the outflow tract are dominant. It is worth noting that one study showed that much higher prevalence of LV from PVC (>20%) versus RV (>10%) was required for the development of CMP that might indicate PVC-induced dyssynchrony as a pathophysiological mechanism. In addition, PVCs of wide QRS (>150 ms) or the ones of epicardial origin are an independent predictor of the development of the CMP<sup>19</sup>.

We noted earlier that the duration of the extrasystoles is an important predictor of the development of CMP. It takes years, not only months for very frequent PVCs to cause the development of CMP. Patients without any symptoms (they visit a doctor later) or those with a length of palpitations >60 months develop cardiomyopathy more often<sup>20</sup>. There is still no unambiguous answer to the question concerning the

## Klinička evaluacija i terapija

VES inducirana karidomiopatija još je uvijek dijagnoza do koje se dolazi isključivanjem. Potrebno je detektirati sve eventualne podležće strukturne bolesti srca koje bi mogle biti uzrok čestim ekstrasistolama. Nekada je vrlo teško utvrditi što čemu prethodi, odnosno koji je primarni poremećaj, ekstrasistolija koja vodi strukturnoj bolesti ili obrnuto. U većine bolesnika nije moguće utvrditi početak učestale ekstrasistolije u odnosu na razvoj CMP<sup>21</sup>. Kako je VES inducirana CMP reverzibilna bolest, važno je pronaći primarni uzrok.

Raspon simptoma kojima se bolesnici prezentiraju proteže se od palpitacija (tipična preskakanja, probadanja, nespecifične prekordijalne opresije), presinkopalnih epizoda, sinkopa pa sve do manifestnog srčanog zatajivanja u slučaju već razvijene karidomiopatije. Kod dijagnoze većina bolesnika ima strukturno zdravo srce<sup>1</sup>, no potrebno je učiniti "standardnu" kardiološku obradu.

Anamnestički je važno ispitati obiteljsku anamnezu (obiteljske neishemijske CMP) te osobnu anamnezu koja može rasvijetliti uzrok eventaulne CMP (toksična, ishemijska — rizični faktori, infektivna itd.). Fizikalnim pregledom najčešće se detektira aritmičan rad srca, ako su VES izrazito česte. U 12-kanalnom elektrokardiogramu mogu se zabilježiti VES što pomaže u lociranju fokusa (najčešće izlazni trakt RV). Isto tako, u EKG treba tražiti naznake aritmogene displazije RV, hipertrofijske kardiomiopatije, itd. Bez 24-, odnosno 48-satnog holter EKG dijagnoza je nemoguća, vrlo je važno odrediti opterećenje bolesnika ekstrasistolijom. Kako je dnevno opterećenje varijabilno, potrebno je češće ponavljati holterski monitoring. Ehokardiografija je nezaobilazna, kako u verificiranju strukturno zdravog srca, tako i u detektiranju najčešćih poremećaja u sklopu ove CMP — dilatacije LV i sniženje EF uz najčešće globalnu redukciju kontraktiliteta<sup>22</sup>. Ehokardiografija nam je također važna u isključivanju drugih eventualnih uzroka CMP te u daljnjem praćenju bolesnika. Još se ne znaju čimbenici rizika za razvoj CMP u sklopu učestalih VES, tako da ne postoje jasne smjernice za učestalost ehokardiografskih kontrola i holterskog monitorniga. Ako postoje čimbenici rizika za koronarnu bolest srca uz regionalne smetnje kontraktiliteta, potrebno je učiniti i koronarografiju. Nadalje, magnetska rezonanca srca može nam dati najbolje podatke ako sumnjamo na aritmogenu displaziju, preboljeli miokarditis ili infiltrativne bolesti srca.

Generalni je konsenzus da je terapija VES potrebna kada je zabilježena disfunkcija LV te postoji temeljita sumnja na VES induciranu CMP, odnosno ako je VES opterećenje izrazito visoko. Terapija je indicirana i u slučaju nešto nižeg VES opterećenja u slučaju izraženih simptoma koji narušavaju kvalitetu života. Postoje dvije terapijske opcije, konzervativno medikamentozno (antiaritmici) liječenje te katerska radiofrekventna (RF) ablacija.

Većina bolesnika s učestalim ekstrasistolama ima strukturno zdravo srce i nakon što smo to utvrdili, ponajprije je potrebno savjetovanje i smirivanje zabrinutog bolesnika, odnosno obrazlaganje da se radi o apsolutno benignom poremećaju s odličnom prognozom<sup>1</sup>. Ne treba žuriti s farmakoterapijom koja je u ovom slučaju indicirana samo ako simptomi ograničavaju bolesnikov život. Prva linija farmakoterapije obično su beta-blokatori ili nedihidropiridinski kalcijски blokatori<sup>23</sup>. U slučaju da oni nemaju efekta mogu se upotrijebiti sotalol ili antiaritmici I.b (meksiletin) ili I.c (propafenon) skupine koji su inače kontraindicirani ako je već razvijena CMP<sup>24</sup>. U ovom slučaju, uvijek treba odvagnuti eventualano proaritmogeno

impact of PVC coupling interval and PVC interpolation on the development of CMP.

## Clinical evaluation and therapy

PVC-induced cardiomyopathy is still a diagnosis of exclusion. It is necessary to detect all potential underlying structural heart diseases that could be a cause for frequent extrasystoles. Sometimes it is very difficult to determine what precedes what, and what a primary disorder is, whether it is extrasystole causing a structural disease or vice versa. In most patients, it is not possible to determine the start of frequent extrasystoles in relation to the development of CMP<sup>21</sup>. As PVC-induced CMP is a reversible disease, it is important to find the primary cause.

The range of symptoms that patients present with, extends from palpitations (typical heart skipping, pricking pains, unspecified precordial oppressions), presyncopal episodes, syncopes to manifest heart failure in the case of already developed CMP. At the time of diagnosis, most of the patients have structurally normal heart<sup>1</sup>, but a standard cardiac work-up should be performed anyway.

It is important to examine family medical history (familial non-ischemic CMP) and the personal medical history that may help explain the cause of any potential CMP (toxic, ischemic — risk factors, infectious, thyroid etc.). Physical examination usually detects arrhythmic heart rate if PVCs are extremely common. The 12-lead electrocardiogram can record PVC which helps locate the focus (most commonly the RV outflow tract). Likewise, the ECG should search for signs of arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy, etc. The diagnosis is impossible without 24-, or 48-hour Holter ECG, because it is very important to determine the patient's PVC burden. As the daily burden varies, Holter monitoring is to be repeated more often. Echocardiography is unavoidable not only in verifying structurally normal heart, but also in diagnosing the most common disorders within this CMP — LV dilatation and global reduction of contractilities<sup>22</sup>. Echocardiography is also important to us to exclude any other potential causes of CMP and for further follow-up of patients. The risk factors for the development of CMP as a part to frequent PVC are still unknown, so that there are no clear guidelines for the frequency of echocardiographic follow-ups and Holter monitoring. If there are risk factors for coronary artery disease with regional wall motion abnormalities, then coronary angiography is to be performed. Furthermore, heart magnetic resonance imaging can give us the best information if you suspect the arrhythmogenic dysplasia, the history of myocarditis or infiltrative cardiac diseases.

The general consensus is that the PVC therapy is required when LV dysfunction is recorded, and there is a thorough suspicious of PVC-induced CMP, or if the PVC burden is extremely high. The therapy is indicated in case of a slightly lower PVC burden in case of pronounced symptoms that impair the quality of life. There are two treatment options, conservative medical (antiarrhythmic drugs) treatment and catheter radiofrequency (RF) ablation.

Most patients with frequent extrasystoles have structurally normal heart and once we determine it, it is primarily necessary to advise and comfort a concerned patient and explain that this it is a completely benign disorder with an excellent prognosis<sup>1</sup>. No need to rush with pharmacotherapy, which is in this case indicated only if the symptoms limit the patient's life. Beta blockers or non-dihydropyridine calcium channel blockers are the first line of pharmacotherapy<sup>23</sup>. In case they have no efficacy, we can use sotalol or I.b antiarrhythmics (mexiletine) or I.c (propafenone) groups which are otherwise

djelovanje antiaritmika, kao i ostale moguće nuspojave naspram potencijalne koristi. U slučaju da liječimo bolesnika kod kojeg je došlo do pada u funkciji LV tada nam, od antiaritmike farmakoterapije, preostaje jedino amiodaron. Terapija amiodaronom se u više studija pokazala kao učinkovita u supresiji VES uz posljedičnu normalizaciju funkcije LV<sup>5,25</sup>.

S obzirom na razvoj novih metoda i opcija invazivnog liječenja aritmija, uključujući 3D navigacijske sustave (koje drastično reduciraju vrijeme fluoroskopije), alternativne izvore ablativne energije (krioablacija), usavršavanje epikardijalnog pristupa itd, kateterska ablacija postaje sve privlačnija opcija liječenja ove bolesti. Još uvijek ne postoje randomizirane kliničke studije koje bi uspoređivale medikamentozno i invazivno liječenje. Unatoč tome postoje brojni izvještaji o uspješnosti RF ablacije u liječenju ove aritmije. Prva grupa koja je izvjestila o uspješnosti RF ablacije u normalizaciji funkcije LV bila je ona od Yarlagadde 2005. godine<sup>14</sup>. Vrlo brzo uslijedilo je više izvještaja sa sličnim rezultatima, na manjim brojevima bolesnika. Najveće serije bolesnika imala je grupa iz Michigena, također s vrlo povoljnim rezultatima RF ablacije. *Bogun i sur.* opisali su 60 bolesnika od kojih je 48 zadovoljavalo kriterije uspješnosti ablacije, a od 22 bolesnika s kompromitoranom funkcijom njih 18 uspješno ablatiranih imalo je značajan oporavak funkcije LV (EF 34% na 59%, LVIDd 59 mm na 51 mm)<sup>6</sup>. *Baman i sur.* su izvjestili o 80% smanjenju VES opterećenja na 174 bolesnika uz značajno poboljšanje funkcije LV (EF 35% na 54%) i redukciju dimenzija LV (LVIDd 59 mm na 54 mm) kod 57 bolesnika koji su imali razvijenu CMP<sup>17</sup>.

Kao i svaki invazivni zahvat, RF ablacija aritmija ima i svoje komplikacije koje se u starijim publikacijama javljaju u do 3% slučajeva, a uključuju moždani udar, AV blok koji zahtjeva elektrostimulaciju, perforaciju, tamponadu, lokalne vaskularne komplikacije, infarkt miokarda, itd<sup>26</sup>. U novijoj literaturi koja se odnosi na ablacije VES, učestalost komplikacija je značajno manja. Zbog navedenog potrebno je dobro razmisliti i odvagnuti potencijalnu korist naspram rizika same intervencije. Ne treba zaboraviti da i medikamentozno liječenje ima svojih negativnih strana, tako da moderne tehnike kateterske ablacije s boljim omjerom rizika i koristi postaju sve primamljivije i češće korištene opcije liječenja VES inducirane karidomiopatije.

## Zaključak

Ventrikulske ekstrasistole su u načelu benigna pojava, osobito ako se radi o strukturno zdravom srcu, no često su previđeni uzrok CMP. S obzirom da se najizglednije radi o dominantno funkcijskom poremećaju koji je u velikoj mjeri reverzibilan, prepoznavanje ovog entiteta je vrlo važno za liječenje dijela bolesnika s neishemijskom CMP. Kateterska radiofrekventna ablacija sve je sigurnija i privlačnija metoda liječenja ovih pacijenata kojom izbjegavamo dugotrajno, moguće i doživotno uzimanje antiaritmika. Stoga, preporučamo da se ovakvi bolesnici referiraju u neki od elektrofizioloških centara.

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contraindicated if CMP has already developed<sup>24</sup>. In this case, you should always weigh any pro-arrhythmogenic effects of antiarrhythmics, as well as any possible side effects against the potential benefits. In case that we treat a patient who has experienced a decline in LV function, then the only one which is left from the antiarrhythmic drug therapy is amiodarone. In a number of studies amiodarone therapy has proved to be efficient in suppressing PVCs which resulted in normalization of LV function<sup>5,25</sup>.

Considering the development of new methods and options of invasive treatment of arrhythmias, including 3D navigation systems (which drastically reduce the time of fluoroscopy), the alternative sources of ablative energy (cryoablation), the advancement of epicardial access etc. the catheter ablation is becoming an increasingly attractive option of treating this disease. There are still no randomized clinical trials that compared the medical and invasive treatment. Nevertheless, there are numerous reports on the success of RF ablation in the treatment of this arrhythmia. The first group which reported on the success of RF ablation in normalizing the LV function was the one from Yarlagadde in 2005<sup>14</sup>. It was followed by some more reports with similar findings on a smaller numbers of patients. The group from Michigan had the largest series of patients, also with very favorable results on RF ablation. *Bogun et al.* have described 60 patients, of whom 48 met the criteria for successful ablation, whereas out of 22 patients with compromised function there were 18 of them successfully ablated who experienced a significant recovery of the LV function (EF 34% to 59% , LVIDd from 59 mm to 51 mm)<sup>6</sup>. *Baman et al.* have reported on 80% reduction of PVC burden in 174 patients with a significant improvement on the LV function (EF 35% to 54%) and reduction in LV dimensions (LVIDd from 59 mm to 54 mm) in 57 patients who had developed CMP<sup>17</sup>.

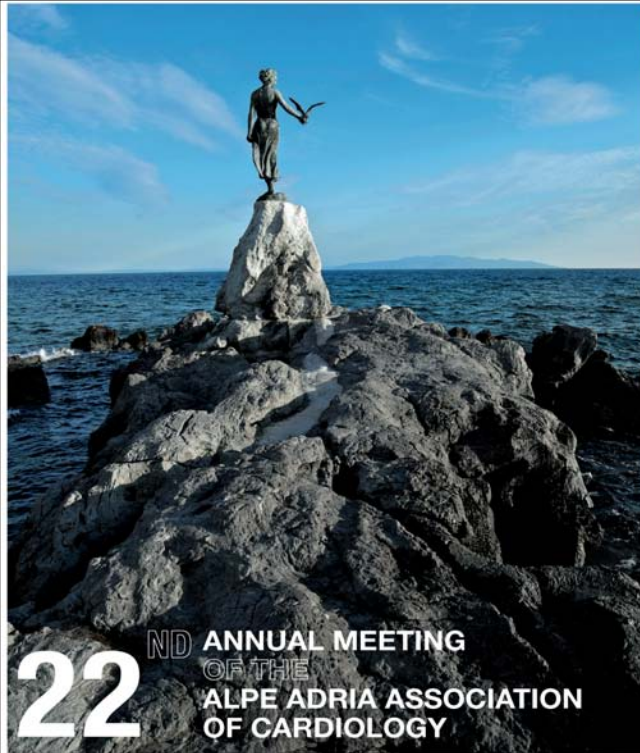
As in case of any invasive procedure, the RF ablation of arrhythmias is followed by its complications which according to previous publications appear in up to 3% of cases and include stroke, AV block requiring electrostimulation, perforation, tamponade, local vascular complications, myocardial infarction, etc<sup>26</sup>. In the recent literature relating to the ablation of PVC, the incidence of complications is significantly lower. For this reason, it is necessary to think it through and weigh the potential benefits and risks of the procedure. We should not forget that the medical treatment also has its disadvantages, so that modern techniques of catheter ablation with a better risk-benefit ratio are becoming increasingly attractive and more commonly used treatment options for PVC-induced cardiomyopathy.

## Conclusion

Ventricular extrasystoles are a common and generally a benign phenomenon, especially if a structurally normal heart is concerned, but they are frequently an overlooked cause of CMP. Given that the most likely scenario is a predominantly functional disorder that is largely reversible, it is very important to recognize this entity for the treatment of one portion of patients with non-ischemic CMP. Catheter radiofrequency ablation is becoming safer and more attractive method of treatment of these patients, where we avoid lengthy, and possibly lifetime antiarrhythmic therapy. Therefore, we recommend that such patients should be referred to some of the available electrophysiology centers.

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