Slovenska aritmologija 2022

SLO Arrhythmias 2022

ZBORNIK PRISPEVKOV
BOOK OF PAPERS

Publikacija je izšla ob letnem znanstveno-strokovnem srečanju pod okriljem delovne skupine za aritmologijo in elektrostimulacijo srca in Združenja kardiologov Slovenije z mednarodno udeležbo / This publication was issued by the annual scientific-professional meeting of the Working Group on arrhythmias and cardiac pacing at Slovenian Society of Cardiology with international participation

Ljubljana, Slovenija
21.–22. oktober 2022
October 21–22, 2022

UREDNIK / EDITOR
Andrej Pernat

IZDALO IN ZALOŽILO / PUBLISHED BY
Združenje kardiologov Slovenije /
Slovenian Society of Cardiology,
Štukljeva cesta 48, 1000 Ljubljana, Slovenija

OBLIKOVANJE IN DTP / COVER DESIGN AND DTP
DSN DESIGN, Maribor, Slovenija

TISK / PRINTED BY
Podgorelec d.o.o., Ljubljana, Slovenija

NAKLADA TISKANE IZDAJE /
CIRCULATION OF PRINTED EDITION
120 izvodov / 120 copies

CIP - Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

616.12-008.318(082)
616.12-085.817(082)

SLOVENSKA aritmologija (srečanje) (2022 ; Ljubljana)
Slovenska aritmologija 2022 = SLO Arrhythmias 2022 : zbornik prispevkov = book of papers : [Ljubljana, Slovenija 21.–22. oktober 2022, October 21–22, 2022] / [urednik Andrej Pernat]. - Ljubljana : Združenje kardiologov Slovenije = Slovenian Society of Cardiology, 2022

ISBN 978-961-6786-37-9
COBISS.SI-ID 126051843

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Delovna skupina za aritmologijo
in elektrostimulacijo srca
Working group on arrhythmias
and cardiac pacing

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OVERVIEW OF INDICATIONS FOR CATHETER ABLATION OF ARRHYTHMIAS

SUPRAVENTRIKULARNE TAHIKARDIJE – PREGLED INDIKACIJ ZA KATETRSKO ABLACIJO

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Uvod

Izraz supraventikularne tahikardije (SVT) tradicionalno zajema vse motnje ritma s srčno frekvenco nad 100/min, razen ventrikularnih tahikardij in atrijske fibrilacije. Večinoma gre za tahikardije z ozkim (pod 120 ms), v nekaterih primerih pa tudi širokim QRS kompleksom. Delimo jih v tri večje skupine: atrijske tahikardije, AV nodalne tahikardije in AV re-entry tahikardije. Omenili bomo najpogostejše.

Vsebina

Pri AV nodalni re-entry tahikardiji (AVNRT) sta v območju AV vozla prisotni dve poti z različno refraktarno dobo, po katerih lahko pride do re-entry tahikardije. Akutno aritmijo lahko prekinemo z vagalnimi manevri ali i.v. aplikacijo adonozina, verapamila ali beta blokatorjev. Ponavljajoča simptomatska AVNRT je indikacija za elektrofiziološko preiskavo, pri kateri se največkrat odločimo za ablacijo počasne AV nodalne poti. Alternativa ablaciji, če se zanjo ne odločimo, je kronična terapija z diltiazemom, verapamilom ali beta blokatorjem.

Pri AV re-entry tahikardiji (AVRT) je prisotna dodatna (akcesorna) AV pot izven območja AV vozla. Prisotnost kongenitalne akcesorne poti, ki lahko vzdržuje tahikardijo, imenujemo sindrom Wolff-Parkinson-White (WPW). Akutno aritmijo lahko prekinemo z vagalnimi manevri ali i.v. aplikacijo adonozina, v primeru neuspešnosti pa pri ortodromni AVRT tudi verapamila ali beta blokatorjev, pri antidromni pa propafenona, flekainida ali prokainamida. Pri pacientih s ponavljajočo simptomatsko AVRT je indicirana ablacija. Alternativa ablaciji, če se zanjo ne odločimo je kronična terapija z beta blokatorjem, verapamilom ali diltiazemom, vendar le ob odstonosti znakov za preekscitacijo (delta val). Pri atrijski fibrilaciji s preekscitacijo se odsvetuje beta blokatorje, diltiazem, verapamin in amjodaron. Pri asimptomatskih bolnikih z znaki za preekscitacijo je indicirana elektrofiziološka preiskava, nujnost ablacije je odvisna od meritev med preiskavo.

Pri fokalni atrijski tahikardiji (AT) aritmijo proži ektopična avtomatska aktivnost. Akutno artimijo lahko prekinemo z i.v. aplikacijo adenozina, beta blokatorjev ali verapamila. Pri ponavljajoči AT je indicirana ablacija, še posebej pri obstojnih AT in znakih tahikardne kardiomiopatije. Alternativa ablaciji, če se zanjo ne odločimo, je kronična terapija z beta blokatorji, verapamilom, diltiazemom, propafenonom ali flekainidom. Pri multifokalni atrijski tahikardiji ablacija ni indicirana.

Pri atrijski undulaciji (AU) gre za makro re-entry tahikardijo, v primeru tipične AU tokokrog poteka okrog trikuspidalnega obroča preko kavotrikuspidalnega istmusa, v primeru atipične AU pa ne. Akutno aritmijo prekinemo z elektrokonverzijo, če se zanjo ne odločimo pa z i.v. aplikacijo amjodarona,

medtem ko se propafenon odsvetuje. Ablacija se svetuje že po eni epizodi tipične AU, še posebej pa po ponavljajočih simptomatskih epizodah.

Ablacija aritmije je indicirana tudi pri vseh SVT s tahikardno kardiomiopatijo in pri ženskah s simptomatskimi ponavljajočimi SVT, ki nameravajo zanositi.

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INDICATIONS FOR CATHETER ABLATION OF ATRIAL FIBRILLATION

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a worldwide prevalence of more than 33 million. AF is frequently associated with stroke, heart failure, and increased mortality. The primary objective of treating patients with AF involve improving symptoms, controlling the rhythm, and reducing the risk of stroke. Emerging data shows that catheter ablation might reduce mortality in patients with heart failure.

Contents

Catheter ablation for AF is a well-established treatment option for patients with symptomatic AF. Current guidelines recommend catheter ablation as a first-line treatment for patients with symptomatic AF regardless of AF type (paroxysmal AF – class IIa; persistent AF without major risk factors for recurrence – class IIb; persistent AF with major risk factors for recurrence – in some circumstance it may be considered as first-line treatment; paroxysmal or persistent AF and heart failure with reduced EF – class I). Catheter ablation is also recommended as a second-line treatment in patients with failed antiarrhythmic drug (AAD) therapy (paroxysmal or persistent AF with or without major risk factors for recurrence – class I; paroxysmal or persistent AF and heart failure with reduced EF – class IIa).

A number of risk factors after AF ablation have been identified, including LA size, AF duration, patient age, renal dysfunction, and substrate visualization with MRI. Many prediction models have been studied; however, no single model has been identified as consistently superior to others in prediction for AF recurrence. Presently, identified risk factors should be considered and tailored to individual circumstances.

The main clinical benefit of AF ablation is the reduction of arrhythmia-related symptoms. Many randomized controlled trials showed a clear benefit of catheter ablation compared with AAD therapy for symptom control. This was confirmed in the CABANA trial, although the primary composite outcome of death, disabling stroke, serious bleeding, or cardia arrest did not reach statistically significant difference.

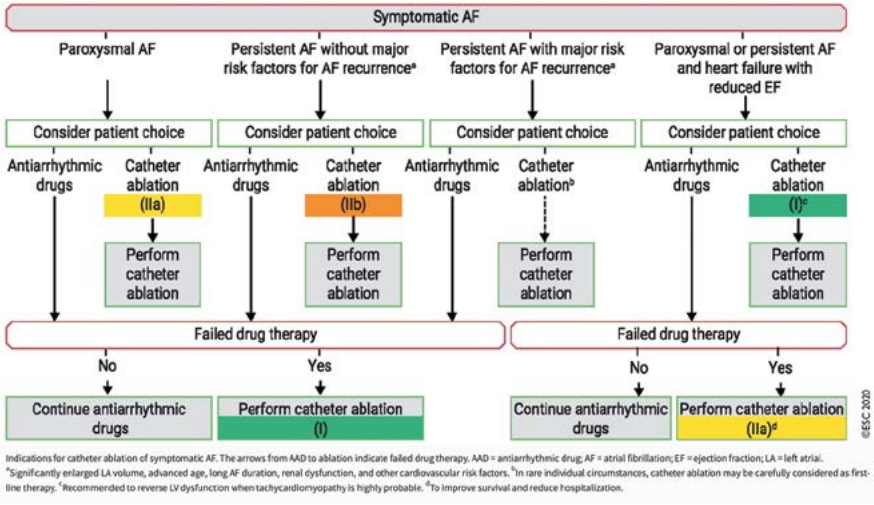
However, EAST-AFNET 4 trial showed that early rhythm control reduced death from cardiovascular causes and stroke. Primary safety outcome did not differ between the early rhythm control group and conventional approach group. However, catheter ablation was only used in 19.4% of patients, 80.6% of patients received AAD therapy.

Following EAST-AFNET4, the EARLY AF showed that cryoablation of symptomatic paroxysmal AF significantly reduced recurrence of symptomatic atrial tachyarrhythmia (11.0 vs 26.2%) without increasing incidence of side effects or serious complications (3.2 vs 4.0%). The multicentric trial STOP AF confirmed finding from EARLY AF trial. Cryoablation of symptomatic AF as a first line treatment significantly reduced the recurrence of atrial tachyarrhythmia (74.6 vs 45.0%).

In selected patient with AF and heart failure with reduced EF catheter ablation was shown to reduce mortality. The CASTLE-AF trials showed significant reduction of mortality (13.4 vs 25.0%). The subgroup analysis of the CABANA, EAST-AFNET4 trials confirmed the findings of the CASTLE-AF trial.

However, recent trial RAFT AF did not show that AF ablation reduces mortality in patient with heart failure with reduced or preserved AF. However, the trial was stopped prematurely because of low enrollment and event rate. Patient in the ablation group had 29% reduction of mortality risk with p value of 0.066. A subgroup analysis of the CABANA trial for patients with preserved EF showed a significant reduction of mortality.

The influence of the aforementioned trials on class recommendation for first-line treatment for symptomatic paroxysmal AF and new indications for catheter ablation in patients with heart failure with preserved EF will be seen in expected 2024 AF management guidelines.



Indications for catheter ablation of symptomatic AF. The arrows from AAD to ablation indicate failed drug therapy. AAD = antiarrhythmic drug; AF = atrial fibrillation; EF = ejection fraction; LA = left atrial. [a]Significantly enlarged LA volume, advanced age, long AF duration, renal dysfunction, and other cardiovascular risk factors. [b]In rare individual circumstances, catheter ablation may be carefully considered as first-line therapy. [c]Recommended to reverse LV dysfunction when tachycardiomyopathy is highly probable. [d]To improve survival and reduce hospitalization.

Take-home message

Catheter ablation is currently indicated only for symptom relief but evidence suggests that it might be indicated for mortality reduction in patients with AF and heart failure.

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INDICATIONS FOR CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

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Introduction

In 2022 new ESC guidelines for the management of patients with ventricular arrhythmias (VA) and prevention of sudden cardiac death (SCD) were presented. While mentioned 276 times in the old guidelines, catheter ablation (CA) was mentioned 367 times in recent guidelines; obviously CA plays an increasingly important role in treatment of VA.

Contents

Generally, VA can be classified according to the presence or absence of structural heart disease (SHD).

In patients with SHD, sustained monomorphic ventricular tachycardias (SMVT) are primarily due to scar-related re-entrant mechanism. While implantable cardioverter defibrillator (ICD) is usually recommended in these patients, it does not prevent VA. The choice of anti-arrhythmic drugs (AAD) in these patients is limited and treatment is frequently hampered by side effects. With the advances made over the last decades, CA has become increasingly important for the management of scar-related VT. For decades CA of bundle branch re-entry VT has been considered as first-line therapy. CA has also been shown to be very effective in controlling incessant VTs or electrical storms and in reducing subsequent VA burden. Many observational studies have shown a positive effect of VT ablation on clinical outcome in terms of VA recurrences. In patients with coronary artery disease (CAD), randomized trials have reported that CA, compared to the conventional treatment, decreases the likelihood of subsequent ICD shocks and prevents recurrent VA episodes. The electrophysiological characteristics of VT circuits depend on the underlying SHD. Thus, post-infarct VTs are mainly related to an endocardial VT circuit (amenable to endocardial ablation), while the location of re-entrant VT circuits is more variable in patients with non-ischemic substrate. Here, mesocardial and/or epicardial involvement are more common. This significantly contributes to the difference in the clinical outcomes of VT ablation in relation to the underlying SHD with a better outcome in CAD as compared to the non-ischaemic aetiologies. The mean long-term success rate of VT ablation varies from 30% to 70%, depending on the underlying SHD.

Idiopathic VA (iVA) is the term for VA that are not associated with SHD or a genetic arrhythmic syndrome. Most iVA are mediated by triggered activity, but a re-entrant mechanism (involving the LV Purkinje network) explains verapamil-sensitive fascicular VTs. Three important key features distinguish iVA from VA associated with SHD. First, iVA mostly originate from a single site and specific region of the heart (namely the right or left ventricular outflow tracts (R/LVOT), along the valve annuli, papillary muscle, or the LV Purkinje network). Second, no detectable scar is found in iVA. Finally, iVA have a

benign prognosis so that ICD implantation is generally not recommended. The earliest site of activation during VT is the ablation target for focal sources, while abnormal Purkinje tissue (with diastolic activity during VT) is the ablation target of left fascicular VTs. CA is curative in most iVA patients.

What is new in 2022

CA is recommended (**I**) for VT ablation in patients with CAD that already have an ICD, are on amiodarone treatment and have experienced recurrent ICD shocks. CA should be considered for patients with CAD and recurrent ICD shocks despite betablocker or sotalol (**IIa**). In patients with CAD and haemodynamically well-tolerated SMVT and LVEF≥40%, CA in experienced centres should be considered as an alternative to ICD therapy, provided that noninducibility and elimination of electrograms consistent with conduction delay is reached (**IIa**). In patients with CAD eligible for ICD implantation, CA may be considered just before implantation to decrease subsequent VA burden and ICD shocks (**IIb**).

In patients with post-myocarditis cardiomyopathy, dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy or Chagas' cardiomyopathy and recurrent SMVT, or ICD shocks for SMVT, in whom AADs are ineffective, not tolerated or desired, CA in specialized centre should be considered (**IIa**).

CA also is also recommended as first-line treatment (**I**) in symptomatic iVA arising from RVOT or left fascicles. In patients with iVA and VA induced cardiomyopathy, CA is also recommended as first-line treatment (**I**) regardless of the location of iVA origin. CA should be considered in patients with symptomatic iVA from an origin other than RVOT or left fascicles (**IIa**). In non-responders to CRT due to frequent monomorphic premature ventricular complex (PVC) catheter ablation or AAD should be considered (**IIa**).

In early repolarization syndrome patients, PVC causing recurrent VF episodes, ablation should be considered when AADs are ineffective (**IIa**). In patients with Brugada syndrome CA of triggering PVCs and/or RVOT epicardial substrate should be considered with recurrent appropriate ICD shocks refractory to AAD (**IIa**), however CA in asymptomatic Brugada syndrome is not recommended (**III**).

In patients with congenital heart disease, symptomatic SMVT or ICD shocks for SMVT not manageable by AAD or ICD reprogramming, CA performed in specialized centres should be considered (**IIa**).

Take-home message

Role of CA in treatment of VA and prevention of SCD has significantly increased in recent years both in SHD and in case of iVA.

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INDIKACIJE ZA ELEKTROSTIMULACIJO SRCA

OVERVIEW OF INDICATIONS FOR CARDIAC PACING

OVERVIEW OF INDICATIONS FOR CARDIAC PACING IN SINUS NODE DISEASE, SUPRAVENTRICULAR TACHYARRHYTHMIAS AND ATRIO-VENTRICULAR CONDUCTION BLOCK

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Introduction

Bradycardia is defined as heart rhythm lower than 60 beats per minute. We are talking about symptomatic bradycardia when the low heart rhythm is combined with symptoms like: syncope, dizzy spells, confusion, seizures, chronotropic incompetence, heart failure, angina pectoris, and sudden death.

The cause of bradycardia is a disturbance in the generation or propagation of an impulse in the heart. The cause of disturbed impulse generation is a disease of the sinus node, and the cause of disturbed impulse propagation is a defect in the conduction system of the heart. Fibrosis, ischemia, structural heart disease, inflammation/myocarditis, medications, electrolyte imbalance, endocrine disturbance are most common causes in adults. In children, bradyarrhythmia can be congenital.

Bradycardia can be persistent or paroxysmal. In paroxysmal type appropriate diagnostic must be performed to prove the correlation between symptoms and arrhythmia.

Sinus node disease

The terms sinus node disease (SND), sick sinus syndrome (SSS), and sino-atrial disease (SAD) are often used interchangeably. All these present a broad range of abnormalities in the sinus node and atrial impulse formation and propagation. SND is manifested as sinus bradycardia, chronotropic incompetence, sinoatrial block, sinoatrial pause and tachy-brady syndrome.

Recommendations for permanent pacing in SND and supraventricular tachyarrhythmias

Permanent pacemaker implantation is indicated for the following situations:
Class I recommendations:

- Pacing is indicated in SND when symptoms can clearly be attributed to bradycardia (level B)
- Pacing is indicated in symptomatic patients with tachy-brady form of SND in order to correct brady-arrhythmias and enable pharmacological treatment, unless ablation of the tachyarrhythmias is preferred (level B).
- In patients with SND and a DDD pacemaker, minimization of unnecessary ventricular pacing through programming is recommended (level A)

Class II a recommendations:
In patients who presents chronotropic incompetence and have clear symptoms during exercise, DDD rate- responsive pacing should be considered (level B)

- AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF – related bradycardia or symptomatic pre-automaticity pause, after AF conversion, taking into account the clinical situations (level B).

Class II b recommendations:

- In patients with the tachy-brady variant of SND, programming atrial anti-tachycardia pacing (ATP) may be considered (level B).
- In patients with syncope, cardiac pacing may be considered to reduce recurrent syncope when asymptomatic pause (s) > 6 s due to sinus arrest is documented (level C).
- Pacing may be considered in SND when symptoms are likely to be due to brady-arrhythmias, when the evidence is not conclusive (level C).

Class III recommendations:

- Pacing is not recommended in patients with bradyarrhythmia related to SND that are asymptomatic or due to transient causes that can be corrected and prevented (level C).

Acquired atrio-ventricular block (AVB)
In the heart, degenerative changes are the main reason for progressive conduction system disease. We distinguish atrioventricular blocks and bundle branch block. Based on electrocardiography (ECG) characteristic, AV block is classified as first, second and third degree. Anatomically, AV block can occur anywhere in the conduction system: above the His bundle, in the His bundle or below.

In the case of atrial fibrillation or flutter, a prolonged pause >5 s is often due to advanced second-degree AV block. Complete AV block manifests as a regular slow < 40/ beats per minute ventricular rate.

In the vast majority of cases, an EKG is useful in determining the level of block, but occasionally an electrophysiological study is required. Certain clinical manoeuvres may be helpful in determining the level of the block. Increased AV conduction with exercise or atropine indicate block at the AV node.

Recommendations for permanent pacing in acquired AV block

Permanent pacemaker implantation is indicated for the following situations:
Class I recommendations:

- Pacing is indicated in patients in sinus rhythm with permanent or paroxysmal third- or second-degree type 2, infra-nodal 2:1 or high-degree AVB, irrespective of symptoms (level C).
- Pacing is indicated in patients with atrial arrythmia (mainly atrial fibrillation) and permanent or paroxysmal third- or high-degree AVB, irrespective of symptoms (level C).
- In patients with permanent atrial fibrillation in need of pacemaker, ventricular pacing with rate-responsive function is recommended (level C).

Class II a reommendations:

- Pacing should be considered in symptomatic patients with second-degree type1 AVB or is found to be located at intra- or infra-His levels at electrophysiology study (level C).

- Permanent pacemaker implantation should be considered for patients with persistent symptoms similar to those of pacemaker syndrome and clearly attributable to first-degree AVB (PR interval >0,3 s) (level C).
- In patients with AVB, DDD pacemaker should be performed over single one to avoid pacemaker syndrome and to improve quality of life (level A).

Class III recommendations:

- Pacing is not recommended in patients with AVB due to transient causes that can be corrected and prevented (level C).

Bundle branch block (BBB)

The ECG shows evidence of conduction delay in both bundles such as complete right-BBB, with or without anterior or posterior hemiblock, or complete left BBB. Chronic BBB is often associated with other heart diseases like ventricular disfunction. Pacing alone can successfully relieve symptoms. It cannot prevent sudden cardiac death, because a ventricular tachycardia may be an alternative mechanism of syncope or sudden death.

Recommendations for permanent pacing in bundle branch block

Class I recommendations:

- In patients with unexplained syncope and bifascicular block, a pacemaker is indicated in the presence of either a baseline His – ventricle (HV) interval of ≥ 70 ms, second- or third-degree intra or infra-Hisian block during incremental atrial pacing, or an abnormal response to pharmacological challenge (level B).
- Pacing is indicated in altering BBB with or without symptoms (Level C).

Class IIb recommendations:

- Pacing may be considered in selected patients with unexplained syncope and bifascicular block without EFS (elderly, frail patients, high-risk and /or recurrent syncope) (Level B).

Class III recommendations:

- Pacing is not recommended for asymptomatic BBB or bifascicular block (level B).

Take-home message

In symptomatic bradyarrhythmic patients, appropriate diagnosis and adherence to recommendations are necessary. This avoids unnecessary pacemaker implantation and complications caused by unnecessary cardiac stimulation.

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INDICATIONS FOR PACING IN PATIENTS WITH DEPRESSED LV FUNCTION

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Introduction

Patients with depressed left ventricular function may need cardiac electrostimulation either due to bradycardia or in the lieu of cardiac resynchronization therapy (CRT). The focus of this contribution is the appropriate selection of device therapy in patients with depressed left ventricular ejection fraction (LVEF) with bradycardia who do not fulfill the guideline criteria for CRT.

Contents

Right ventricular pacing (RVP) represents a standard pacing option for patients with bradycardia. While it satisfies its role in the reversal of bradycardia, it induces non-physiological activation of the left ventricle, which results in electrical and mechanical dyssynchrony. Long-term RVP with a high percentage of ventricular pacing may consequently lead to the reduction of LVEF and the development of pacing-induced cardiomyopathy (PICM). It has been shown that every 10% increase in RVP increases the risk of heart failure hospitalization by 20%. The risk for the development of PICM is higher in patients who already present with reduced ejection fraction at the time of device implant.

Recent ESC guidelines for cardiac pacing and resynchronization recommend the selection of CRT instead of RVP in patients with LVEF below 40% (HFrEF patients) regardless of NYHA class (class I, level of evidence A). The cornerstone for this indication was the BLOCK HF trial which randomized 691 patients with LVEF below 50% into RVP and CRT. After a follow-up of 37 months, CRT reduced the primary endpoint of all-cause death, urgent care visits due to heart failure and negative left ventricular remodeling (HR 0.73) as well as hospitalizations due to heart failure (HR 0.68). While the development of PICM is not confined to patients with HFrEF and may occur even in 12.3% of patients with preserved LVEF, there is no guideline recommendation for CRT in patients with bradycardia and HFmrEF. However, His bundle pacing (HBP) may be considered in patients with atrioventricular block and anticipated > 20% of ventricular pacing (class IIb, level of evidence C).

While the guidelines recommend the substitution of RVP for CRT, recent observational trials in unselected patients requiring bradycardia pacing demonstrated favorable outcomes with HBP and left bundle branch area pacing (LBBAP) when compared to RVP. While both conduction system pacing techniques reduced the incidence of PICM and heart failure hospitalizations, LBBAP also demonstrated a reduction in mortality. However, while there were small randomized trials that demonstrated the comparable outcomes between CRT, HBP and LBBAP in patients with indication for CRT, to date there has been no randomized trial for bradycardia indication.

Patients who develop PICM after RVP may be candidates for CRT upgrade. While there has been no randomized trial, observational trials and meta-analysis showed a comparable reduction in mortality, heart failure hospitalizations and echocardiographic response as in patients with de novo CRT implantation. However, in contrast with de novo CRT in patients with bradycardia and HFrEF, guidelines indicate an upgrade to CRT only in patients with EF≤35% who remain symptomatic despite OMT (class IIa, level of evidence B).

A recent randomized trial by Brignole et. al showed a remarkable survival benefit (HR 0.26) with atrioventricular junction (AVJ) ablation and CRT in patients with symptomatic heart failure and permanent atrial fibrillation despite the controlled heart rate even in the medically treated group. The current ESC guidelines recommend CRT (class I, level of evidence B) in patients with AVJ ablation and HFrEF and HFmrEF (class IIa, level of evidence C), but allow CRT to be considered even in patients with preserved LVEF (Class IIb, level of evidence C).

Take-home message

Right ventricular pacing induces electrical and mechanical dyssynchrony, which may be especially detrimental in patients with reduced LVEF. In these patients, especially in those with LVEF<40%, even if asymptomatic, CRT should be considered as an alternative to RVP. In patients with LVEF>40% and an anticipated high percentage of ventricular pacing conduction system pacing may be considered.

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INDIKACIJE ZA BREZELEKTRODNO ELEKTROSTIMULACIJO

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Uvod

Današnji običajni srčni spodbujevalniki so sestavljeni iz pulznega generatorja in elektrodnih vodov. Elektrodni vodi so od pulznega generatorja do votline desnega prekata speljani preko vene, običajno podključnične vene. Brezelektrodni spodbujevalnik je v primerjavi z običajnimi spodbujevalniki precej manjši, ne potrebuje elektrode, saj se vstavi neposredno v srce (slika 1). Tako se izognemo vsem zapletom, ki se pojavijo zaradi elektrodnega katetra (dislokacija, penetracija, perforacija elektrode). V telesu je manj tujega materiala, ni kovin, zato je primeren tudi za bolnike, ki so alergični na kovino, za kar do zdaj ni bilo prave alternative. Zaradi majhnosti naprave ni motečih estetskih posledic. Za vstavitev v bolnika nista potrebna vrez kože in priprava ležišča, kamor bi bil vstavljen običajni srčni spodbujevalnik. S pomočjo uvajala (23 F) brezelektrodni spodbujevalnik preko dimeljske vene vstavimo v votlino desnega prekata. S tem se izognemo poškodbi tkiva in pojavu razjed, ki vodijo do okužbe operacijske rane, krvavitvam in hematomu na mestu vsaditve. Pri proceduri vstavljanja se povsem izognemo predrtju površine pljuč – pnevmotoraksu. Bolnik lahko varno opravi tudi slikanje z magnetno resonanco, pri jakosti magnetnega polja 1,5 T in 3 T. Bolniki brez gornjega venskega pristopa do srca ne morejo dobiti običajnega srčnega spodbujevalnika. Trenutna alternativa je epikardialna vstavitev spodbujevalnika, katera zahteva kirurški poseg v splošni anesteziji, torakotomijo.

Slika 1. Brezelektrodni srčni spodbujevalnik nameščen v desnem prekatu

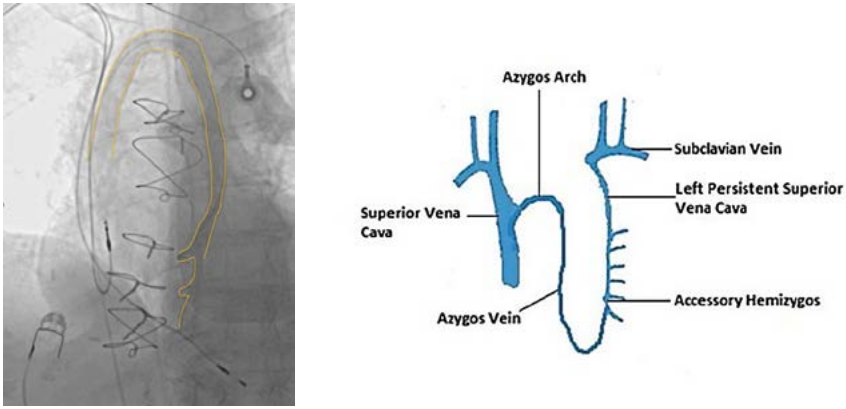
Čas hospitalizacije in čas postoperativnega okrevanja bolnika se znatno podaljšata, pomembno se povečajo tudi stroški zdravljenja, bolniku pa se zmanjša kvaliteta življenja, saj so epikardialne elektrode dokazano bolj občutljive za poškodbe in posledično zahtevajo več zamenjav v času bolnikovega življenja. Običajni srčni spodbujevalnik lahko predstavlja tudi problem bolnikom z bolj aktivnim življenjskim

slogom, zlasti pri premikanju rok in dvigovanju težjih bremen. Izognemo se tudi twiddlerjevemu sindromu, kjer se zaradi ohlapnega ležišča in prevelike aktivnosti bolnika, vstavljeni spodbujevalnik prične rotirati okoli svoje osi ter navija elektrodni kateter okoli sebe. Zdravljenje zahteva odstranitev ovitega elektrodnega katetra in ponovno vstavitev na primerno mesto (1-3).

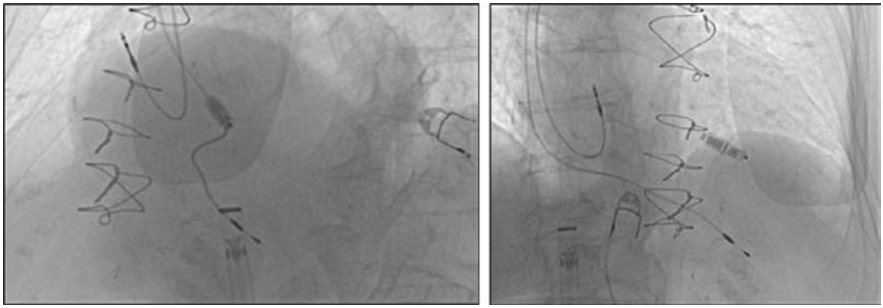
Bolniki primerni za brezelektrodno spodbujanje

V Sloveniji zdravimo z elektrostimulacijo srca do 1600 bolnikov letno. Prednost takšnega načina zdravljenja je v dokončni ozdravitvi bolnika, saj z elektrostimulacijo srca v celoti nadomestimo manjkajoče srčne utripe. Vseeno pa pri cca 10% bolnikov naletimo na naslednje težave:

- ni žilnega dostopa (anomalija ven, stanje po operacijah, stanje po večkratni menjavi baterij, dializni bolniki) (slika 2 in 3)
- infekcije v področju spodbujevalnika (v tem primeru je ponovna vsaditev enakega sistema tvegana)
- alergije na kovino (alergične reakcije, zavrnitev telesa)



Slika 2. Levo: Bolnik z vstavljenim DDD spodbujevalnikom, okvaro prekatne elektrode in okluzijo desne in leve podključnične vene. Desno: Shematski prikaz anatomske variante.



Slika 3. Vstavljen brezelektrodni spodbujevalnik pri zgornjem bolniku. Levo pogled LAO, desno pogled RAO.

V teh primerih je potrebno dodatno ukrepanje, poleg dolgotrajnega antibiotičnega zdravljenja so v kasnejši fazi potrebni operativni posegi, s pomočjo katerih namestimo srčni spodbujevalnik, največkrat elektrode prišijejo na površino srčne mišice, seveda pa je zato potrebno odpreti prsni koš. Poleg izrazitega nelagodja za bolnika gre pri tem tudi za naraščanje stroškov zaradi več zaporednih posegov.

Brezelektrodni spodbujevalnik v Sloveniji

V UKC Ljubljana smo brezelektrodni spodbujevalnik prvič vstavili decembra 2017. Do sedaj smo vstavili 40 takšnih naprav, večinoma pri starejših bolnikih z atrijsko fibrilacijo in kontraindikacijo za običajno spodbujanje. Do nedavnega je bila uporaba brezelektrodnega spodbujanja omejena na enokomorno spodbujanje (ti. VVI način), od leta 2020 pa obstaja tudi možnost sinhrone (ti. VDD) stimulacije, kar pomeni zlasti boljšo hemodinamsko učinkovitost spodbujevalnega sistema kot tudi širši nabor bolnikov. Tudi na tem področju imamo že začetne izkušnje. Brezelektrodni AV spodbujevalnik zagotavlja VDD-spodbujanje, ki temelji na mehanskem atrijskem zaznavanju z uporabo 3-osnega ekcelerometra.

Enokomorni brezelektrodni spodbujevalnik (VVI)

Zaradi vsega navedenega so na voljo posebne naprave brez elektrod, ki se s pomočjo uvajala (23 F) preko dimeljske vene vstavijo v votlino desnega prekata. Spodbujevalnik je v obliki valja, dolžine 25 mm, debeline 4,99 mm. Pritrditev na endokard je možna s pomočjo posebnega mehanizma iz titanija, ki stabilizira spodbujevalnik na željenem mestu. Spodbujevalnik lahko v primeru neustreznega položaja s posebno zanko zopet odstranimo in ga prestavimo na ustreznejše mesto. Komunikacija s spodbujevalnikom poteka s pomočjo običajnega programatorja za srčne spodbujevalnike z dodatkom posebne vmesne enote (4-5). Pogoji elektrostimulacije so enaki kot pri običajnem spodbujevalniku, trenutno pa pričakovana življenjska doba spodbujevalnika znaša okoli 10 let, odvisno od pogostnosti stimulacije. Za tak postopek spodbujanja so zaenkrat primerni le bolniki, ki potrebujejo enokomorni spodbujevalnik (6).

Brezelektrodni spodbujevalnik z možnostjo AV (preddvorno-prekatne) sinhronosti

Uporaba transvenskih enokomornih srčnih spodbujevalnikov je omejena na <15% populacije bolnikov, ki potrebujejo spodbujevalnik. Bolniki s sinusnim ritmom in atrio-ventrikularnim blokom pa pridobijo več z dvokomornim srčnim spodbujevalnikom, ki lahko zagotavlja AV sinhronizacijo. V ta namen so raziskovalci v že uveljavljeni in klinično uporabljeni brezelektrodni spodbujevalnik vgradili poseben algoritem, ki zaznava atrijske kontrakcije z vgrajenim 3-osnim merilnikom pospeška. Rezultati zgodnjih raziskav so pokazali, da je atrijsko zaznavanje na merilniku pospeška izvedljivo in je znatno izboljšalo AV sinhronizacijo. Na podlagi rezultatov študije MARVEL (Micra Atrial tRacking using a Ventricular accELerometer) so algoritme še izboljšali, vključno z avtomatiziranimi funkcijami programiranja in algoritmi za preklapljanje načina stimulacije s ciljem prilagajanja spremembam v pacientovem ritmu in aktivnosti. V raziskavi MARVEL 2 je bila prisotna več kot 70% sinhronost pri več kot 95% bolnikov v fazi mirovanja, prav tako je bil ustrezno temu povečan tudi utripni volumen (7-11).

Brezelektrodni resinhronizacijski spodbujevalnik

Brezelektrodni resinhronizacijski spodbujevalnik (naprava WiSE CRT; EBR Systems, Sunnyvale, CA) je sestavljen iz sprejemne elektrode v levem prekatu, ki je vsajena transkatetrsko, ultrazvočnega oddajnika, ki ga implantiramo kirurško v akustičnem oknu (običajno v peti ali šesti medrebrni prostor) in baterije. Med sprejemno elektrodo in ultrazvočnim oddajnikom obstaja neprekinjena komunikacija, na katero ne sme vplivati položaj bolnika ali dihanje. Oddajnik je povezan z baterijo, ki je vsajena v podkožje. Stimulacija endokarda levega prekata je bolj fiziološka kot epikardialna stimulacija iz področja koronarnega sinusa. Poleg tega je možna poljubna izbira mesta endokardialne stimulacije levega prekata. Nedavno objavljeni register 90 bolnikov iz 14 evropskih držav je pokazal uspešnost vsaditve naprave v 94,4% bolnikov, ter izboljšanje klinične slike pri skoraj 70% bolnikov (12).

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INDICATIONS FOR PACING IN PEDIATRIC POPULATION

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Introduction

The purpose of this document is to provide information regarding the management of pediatric patients with symptomatic bradycardias, with a primary focus on the pacing indications. This age-specific document, based on already published guidelines, underlines different indications for pacing as well as size-specific technology factors in younger patients.

Pacing indications in pediatric patients

The most common indications for permanent pacemaker (PPM) implantation in children, adolescents, and patients with congenital heart disease (CHD) may be classified as 1) symptomatic sinus bradycardia, 2) advanced second- or third-degree AV block, either congenital or acquired, and 3) pacing for the prevention or termination of tachyarrhythmias. In general, many of the indications for pacemaker implantation in children and adolescents are similar to those in adults. However, there are several important differences in infants and children. These patients have faster heart rates, and therefore standards for what is considered normal are age-dependent variables. Although the average ventricular rate in newborns and infants with congenital complete atrioventricular block provides an objective measure regarding the decision for pacemaker implantation, additional factors may equally influence the decision on timing of PPM implantation. These factors include birth weight, congenital heart defects, ventricular function, and other comorbidities. It is important to underline that young patients with impaired ventricular function or abnormal cardiovascular physiology may be symptomatic due to sinus bradycardia or loss of atrioventricular (AV) synchrony at heart rates that do not produce symptoms in individuals with normal cardiovascular physiology. Therefore, establishing a temporal correlation between symptoms and bradycardia is critical in the decision as to whether PPM is indicated. Significant technical challenges may complicate device and lead implantation in small patients or those with abnormalities of venous or intracardiac anatomy. Epicardial pacemaker lead placement and use of device technology in innovative ways often need to be considered to provide pacing in the youngest patients. Of note, any pacemaker system used in a young patient may need to be utilized for multiple decades. Therefore, consideration of the long-term consequences from device and lead failure, as well as the consideration regarding ventricular synchrony depending on the site of the ventricular pacing, play an important role in clinical decisions. Conduction system pacing is the new pacing modality in pediatric population, that could ensure better long-term clinical outcomes as it preserves left ventricular synchrony. However, long-term data and improvement of delivery tools are needed for wider clinical adoption.

Take-home message

As the pediatric and CHD populations represent unique groups of patients, clinical judgment and patient-specific decision-making are of great importance. Apart from bradycardia indications, several additional factors need to be considered for optimal clinical decisions on timing and method of PPM implantation. Conduction system pacing could represent a feasible pacing modality in pediatric patients; however, long-term data and improvement of delivery tools are needed for wider clinical adoption.

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OBRAVNAVA ZAPLETOV SRČNE ELEKTROSTIMULACIJE

MANAGEMENT OF IMPLANTED CARDIAC PACING DEVICES RELATED COMPLICATIONS

COMPARISON OF DIFFERENT VASCULAR APPROACHES IN CARDIAC PACING IMPLANTATION PROCEDURE

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Introduction

Cardiac implantable electronic devices (CIED) are the mainstream therapy for a variety of patients with bradyarrhythmia as well as those at risk of sudden cardiac death and heart failure. Despite sometimes being lifesaving, the implant is surgical and therefore carries all the inevitable intrinsic risks. In the process of technology evolution, one of the most important factors is to make it safer for the patient. The first stage begins by gaining central venous access for lead insertion. Techniques for central venous access can be divided into two categories: requiring direct visualisation of the target vein with subsequent venesection (most commonly the cephalic vein) and requiring venepuncture (most commonly conventional subclavian vein puncture and axillary vein puncture). Less commonly utilised approaches include access through the internal or external jugular vein with the lead tunnelled over/under the clavicle to the generator. It is possible to insert the leads via the iliofemoral vein as well; this approach was historically used when it was impossible to access the heart via SVC branches.

Contents

Cardiovascular implantable electronic device (CIED) implantation has become a widespread procedure with a broad range of indications, including restoring atrioventricular synchrony, providing sudden death protection, and improving cardiac function through cardiac resynchronization therapy. Venous access is a critical part of this kind of procedure, and numerous techniques are available to reach central venous circulation.

The right or left cephalic vein is the most common vascular entry site for insertion of CIED leads by cutdown technique. Cephalic vein access has the advantage of avoiding pneumothorax and reducing the risk of lead dysfunction compared to subclavian puncture. Successful cannulation is reported in approximately 60–80% of patients.

However, this technique requires some surgical skills, and in most cases, there is not room for 2 or 3 leads inside a cephalic vein. Bleeding complications are not significantly different compared to subclavian access. Supra-clavicular course of the vein is a rare variant that should be recognized.

Subclavian vein puncture using the Seldinger technique allows easy access to the central circulation but requires an intrathoracic needle pathway, leading to the risk of pneumothorax, hemothorax, and lead insulation damage (subclavian crush sy). Friction with the clavicle, subclavius muscle or costo-clavicular ligament may also restrict lead manipulation and positioning. Subclavian access has been associated with a higher risk of bleeding complications in patients receiving antiplatelet drugs. Other rare complications include arterio-venous fistula, transient phrenic nerve palsy due to local anaesthesia, and thoracic duct injury. For these reasons, it is recommended that

subclavian vein puncture is not used as a first-line approach, but as abailout technique in case other routes have failed, or for venous access medial to occlusions.

In the past few years, the axillary vein has become the target for needle access for CIED implantation due to its easy accessibility, extrathoracic course, and very predictable anatomy. Axillary vein approach seems to be a favourable technique not only for the prevention of acute complications but also to reduce lead failure including lead insulation and lead fracture prevention with a consequently better long-term lead survival compared with the classical subclavian approach. Various techniques of axillary vein puncture have been proposed ranging from a blind percutaneous puncture to the use of different tools such as contrast venography and ultrasound.

	Extrathoracic subclavian; axillary	Cephalic	Conventional subclavian
Vein present	Almost always	Not always	Almost always
Surgical skill required	Average	Most skill needed	Average
Procedure time	Average	May be prolonged	Average
Blood loss	Minimal	May be more significant	Minimal
Risk of air embolism	Higher	Minimal when the lead is passed directly into the vein (due to presence of venous valves)	Higher
Risk of pneumothorax	<0.1%	<0.1%	1–2%
Risk of arterial puncture	Low	Very low	The highest
Risk of thoracic duct puncture	Very low	Absent	The highest
Risk of lead crush	Higher	Very low	The highest
Amount of fluoroscopy required	The highest	Minimum	Low
Passage of multiple leads	The easiest	May be difficult. Friction between adjacent leads may make manipulation difficult and cause accidental lead dislodgement	Easier
Extraction of chronic leads from this access	Easier	Can be difficult and have more difficult haemostatis[3]	Easier
Anatomical variations	More variable More caudal in whites More cranial in men and patients with higher BMI	The most variable Can be present as venous plexus rather than a single vein Can be very deep in overweight patients May occasionally drain into the jugular vein	The least variable

Take-home message

Central venous access that is minimally invasive and safe is imperative for lead insertion of CIEDs such as permanent pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy. Each approach has its advantages and disadvantages. Operators may have greater comfort and expertise with one approach or another, but they should be familiar with more than one technique to have a backup option if the favourite fails.

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PREPOZNAVA IN OBRAVNAVA PREMIKA ALI POŠKODBE ELEKTROD ZA SRČNO SPODBUJANJE

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Uvod

Premiki in poškodbe elektrod za srčno spodbujanje so poleg krvavitev in pnevmotoraksa najpogostejši zapleti po operativni vstavitvi naprav za srčno spodbujanje. Pomembno je, da v primeru suma na premik elektrode le-to potrdimo s pravimi diagnostičnimi metodami in ukrepamo preden pride pri pacientu do ogrožujočih kliničnih znakov.

Premik elektrode (angl. lead dislocation, displacement, dislodgement) pomeni kakršnokoli spremembo položaja elektrode, klinično pomembni pa so tisti premiki, ki povzročijo nepravilno delovanje srčne naprave. Poškodba elektrode je izguba integritete kateregakoli dela elektrode zaradi delovanja zunanjih sil, običajno ločimo poškodbe vodnika in/ali izolacije elektrode.

Epidemiologija

Ločimo zgodnje premike znotraj prvih 6 tednov po implantaciji in pozne premike, ki se zgodijo kasneje. Zgodnji premiki so pogostejši in so najpogostejši vzrok za ponoven operativni poseg.

V veliki nemški študiji, ki je vključevala čez 400.000 implantacij srčnih spodbujevalnikov v obdobju 6 let, je bila incidenca premikov prekatne elektrode 0,92%, preddvorne elektrode pa 1,22%. Največji vpliv na incidenco je imelo število implantacij v posamezni bolnišnici: incidenca premikov elektrod v bolnišnicah z do 50 implantacijami na leto je bila več kot dvakrat večja kot v bolnišnicah z nad 190 implantacijami letno. Relativno bolj pogosti kot premiki elektrod za desni preddvor in prekat so sicer premiki elektrode za levi prekat pri biventrikularnih spodbujevalnikih in defibrilatorjih.

V zadnjih letih se je število dislokacij elektrod pomembno zmanjšalo na račun prevladujoče uporabe aktivnih elektrod, ki omogočajo bolj zanesljivo fiksacijo konice elektrode in lažjo odstranitev elektrode, če je to potrebno.

Premik preddvorne elektrode povzroči nezanesljivo zaznavanje in/ali stimulacijo v preddvoru, kar je lahko klinično nemo. Premik prekatne elektrode je bolj redek, a potencialno bolj nevaren, saj pri od spodbujevalnika odvisnih pacientih lahko pride do hude bradikardije ali asistolije.

Etiologija

Vzrok za premik elektrode največkrat ni znan, sklepamo lahko, da fiksacija ni bila dovolj zanesljiva. V posebnih primerih je vzrok jasen, kot npr. pri Twiddlerjevem ali Reelovem sindromu pri katerih premik elektrode nastane zaradi navijanja le-te okrog generatorja srčne naprave, ki ga pacient vrti okoli osi.

Poškodbe elektrod so redkejše od dislokacij. Poškodba prsnega koša v predelu generatorja spodbujevalnika ali elektrod lahko povzroči poškodbo elektrode, poškodbo generatorja ali premik elektrode. Poškodba elektrode (vodnika ali izolacije) najpogosteje nastane zaradi prekomernega pritiska na mestu fiksacije s šivom ali prehoda med ključnico in rebrom.

Diagnostika

Klinična slika pri premiku ali poškodbi elektrode je odvisna od pacientove odvisnosti od stimulacije, vrste premaknjene elektrode (preddvorna, za levi ali desni prekat), pogostosti izgube učinkovite stimulacije in končnega položaja elektrode po premiku. Občasna ali trajna odsotnost učinkovite stimulacije je lahko asimptomatska (predvsem v primeru preddvorne in elektrode za levi prekat), lahko pa pride do pomembnih bradikardij in asistolij z omoticami ali izgubami zavesti. Posledica premika elektrode je lahko stimulacija izvensrčnih struktur npr. freničnega živca ali prepone.

Za potrditev premika elektrode uporabimo tri diagnostične metode:

- Z **EKG** ugotavljamo prisotnost ali odsotnost zaznavanja, prisotnost in učinkovitost stimulacije posameznih votlin, motnje so lahko intermitentne ali stalne.
- Z **RTG prsnih organov v dveh projekcijah** presojamo ustreznost položaja posameznih elektrod. Pri tem upoštevamo običajne položaje elektrod ob implantaciji, najbolj zanesljiva je primerjava z izhodiščnim RTG posnetkom. Glede na RTG posnetek ločujejo dve vrsti premika: makro premik (macro-displacement), ki je viden na RTG posnetku in mikro premik (micro-displacement), ki ni zaznaven na RTG posnetku, saj gre za minimalen premik (odmik) konice elektrode za največ nekaj milimetrov.
- S **programatorjem za srčne naprave** pri sumu na premik elektrode iščemo značilne spremembe izmerjenih vrednosti impedance in praga draženja glede na izhodiščne vrednosti (Tabela 1.) Premik elektrode se odraža tudi v spremembah zaznavanja, bolj kot sprememba amplitude je pomembna sprememba razmerja med zaznavanjem preddvornega in prekatnega signala, npr. pri premiku preddvorne elektrode kavdalno se v signalu poveča amplituda R vala. Ker je po premiku elektrode položaj le-te lahko nestabilen, je možna velika variabilnost izmerjenih parametrov oz. intermitentne motnje zaznavanja in stimulacije.

Tabela 1. Izmerjeni parametri elektrode za spodbujanje pri različnih vrstah disfunkcije elektrode. (povzeto po Fuentes B., et al.)

Vrsta disfunkcije	Prag draženja	Impedanca
Normalno delovanje	normalen	normalna
Makro premik elektrode	povišan	znižana
Mikro premik elektrode	povišan	normalna
Prekinitev vodnika elektrode	povišan	povišana
Poškodba izolacije elektrode	normalen	znižana

Zdravljenje

Način zdravljenja oz. poprave premika elektrode je odvisen od več dejavnikov, najpomembnejša sta čas od implantacije in klinična slika oz. stopnja disfunkcije, poleg tega še tip elektrode (aktivna ali pasivna), položaj elektrode (preddvor ali prekat), vrsta indikacije za spodbujanje oz. odvisnost od srčne naprave, splošno stanje pacienta.

Čas od implantacije je pomemben zaradi možnosti za popravo položaja premaknjene elektrode. Pri zgodnjih premikih je indicirana operativna repozicija premaknjene elektrode, pri poznih ali pozno ugotovljenih premikih pa je lahko elektroda že fiksirana in položaja ni mogoče popraviti, kar posebej velja za pasivne elektrode. Aktivne elektrode je mogoče mobilizirati in položaj popraviti še več mesecev ali let po implantaciji. Če poskus mobilizacije ni uspešen je potrebna vstavitev dodatne elektrode. Obstaja tudi možnost odstranitve premaknjene elektrode s postopki za ekstrakcijo elektrod. Enake postopke uporabimo pri poškodbi elektrode. Disfunkcijo atrijske elektrode pri bolnikih s kratkim pričakovanim preživetjem ali drugimi zadržki za operativni poseg lahko obravnavamo konzervativno s programiranjem spodbujevalnika v način delovanja VVI.

Preventiva

Ustrezno izvedeni postopki pri implantaciji srčne naprave so najpomembnejši preprečevalni ukrep za premik ali poškodbo elektrod: priprava ustreznega (ne prevelikega) podkožnega žepa za srčno napravo, kar omogoča imobilizacijo naprave, po potrebi prišitje generatorja oz. uporaba implantacije pod prsno mišico, uporaba aktivnih elektrod, ustrezna fiksacija elektrod na vstopnem mestu v veno. Pomembno je tudi obnašanje pacienta v obdobju celjenja rane z izogibanjem pretiranih obremenitev in skrajnih gibov zgornje okončine na strani implantacije.

Večina premikov elektrode se zgodi zelo zgodaj po implantaciji, zato je poleg preventive zelo pomembno zgodnje ugotavljanje zapleta, kar dosežemo z RTG posnetkom prsnih organov v 24-48 urah po vstavitvi in testiranjem delovanja srčne naprave s programatorjem. Preostale premike lahko ugotovimo ob prvi ambulantni kontroli s programatorjem 1-3 mesece po implantaciji. Na ta način lahko večino premikov ugotovimo v zgodnjem obdobju, ko je korekcija položaja elektrode še razmeroma enostavna.

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PREPREČEVANJE IN OBRAVNAVA HEMATOMA ŽEPA NAPRAV ZA SRČNO SPODBUJANJE

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Uvod

Letno se v zahodnem svetu vstavi približno 1000 vgradnih električnih naprav (CIED) na 1000000 prebivalcev. Prejemniki vsadnih naprav so pogosto polimorbidni bolniki z bolezenskimi stanji, ki zvišujejo tveganje za krvavitev (KLB, trombocitopenija, koagulopatija, jetrne bolezni, visoka starost). Ti bolniki jemljejo različne kombinacije zdravil, 40% jih je na antikoagulantnih in 57% na antiagregacijskih zdravilih. Obe vrsti zdravil sicer zmanjšujeta tveganje za ishemične in trombembolične dogodke vendar hkrati povečujeta tveganje za periproceduralno krvavitev. Še posebej je tvegana kombinacija ASA in P2Y12. Najpogostejši vaskularni zaplet pri vstavitvi CIED je hematom žepa, ki se pojavi pri 1- 4% primerov. Ostali zapleti so redkeješi (hematotorax, tamponada 0,1-0,8 %). Hematom žepa se izraža pretežno z oteklino in lokalno bolečnostjo. Posledice se kažejo z daljšo hospitalizacijo in višjimi stroški zdravljenja, podaljšanim obdobjem brez antitrombotične terapije predvsem pa višjim tveganjem za okužbo in posledično večjo umrljivostjo.

Vsebina

Hematom žepa skušamo zdraviti konzervativno. Za revizijo oz. evakuacijo (nikoli punkcijo!) hematoma se odločimo izjemoma zaradi visokega tveganja za okužbo. Glede na tip CIED je višja verjetnost pojava hematoma pri vstavitvi kompleksnih naprav npr. CRT(D) in ICD ter pri nadgradnjah ali menjavah sistemov in reviziji z vstavitvijo dodatnih elektrod. Strategija periproceduralne premostitve antagonistov vitamina K (VKA) z heparinom predstavlja pomembno višje tveganje za krvavitev, kot ob jemanju izključno VKA, kar potrjujejo rezultati študiji Bruise control in Bridge. Glede na spoznanja izhajajočih iz raziskav opravljenih v zadnjih 10 letih je premostitev z heparinom odsvetovana. Pri bolnikih z visokim tveganjem za trombemboličen dogodek (umetne valvule, VTE znotraj 3 meseci, AFS, CHADS Vasc score 5 in več, CVI ali TIA znotraj 6 mesecev) se poseg opravi brez prekinitve VKA ob INR znotraj terapevtskega območja. V kolikor je bolnik na novih antikoagulantih (NOAK) le ti ne predstavljajo velikega tveganja za krvavitve. Glede na rezultate študije Bruise 2 ni bilo signifikantnih razlik v pojavnosti hematoma žepa med kontinuiranim jemanjem ali prekinitvijo v periproceduralnem obdobju. Pri odločitvi o prekinitvi se upošteva ledvično funkcijo, vrsto NOAK in preferenco operaterja. Glede na podatke iz metaanaliz se pojavljajo krvavitve pri dvojni antiagregacijski terapiji 4-5x , medtem ko pri aspirinu pa 1,5-2 x pogosteje kot brez antiagregacijske terapije. Zato se svetuje prehodna opustitev P2Y12, razen v kolikor je od PCI minilo manj kot 1 mesec ali od AKS manj kot 6 mesecev,. Pri posegih z visokim tveganjem (npr. revizija elektrode, nadgradnja oz. menjava aparata) pride v poštev pri skupini bolnikov z najvišjim tveganjem za trombozo stenta premostitev z GP IIb/IIIa ali cangrelorjem ob aspirinu. Analiza študij BUISE CONTROL -1 IN 2 je dokazala 10% pojavnost hematoma žepa pri bolnikih na kombinirani antikoagulantni in

antiagregacijski terapiji, zato naj bi se poseg opravil ob prehodni opustitvi bodisi antikoagulantne ali antiagregacijske terapije.

Ključno sporočilo

Hematom žepa je najpogostejši zaplet vstavitve CIED. Pomemben je tako s kliničnega kot finančnega vidika. Za zmanjšanje tveganja krvavitve je poleg izkušenosti operaterja ter ustrezne operativne tehnike potrebna tudi individualna priprava bolnika na poseg glede na oceno tveganje za krvavitve in ishemičen oz. trombemboličen dogodek.

PREPREČEVANJE, DIAGNOSTIKA IN ZDRAVLJENJE OKUŽB NAPRAV ZA SRČNO SPODBUJANJE

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Uvod

Srčni spodbujevalniki (PM), implantabilni srčni defibrilatorji (ICD) in naprave za srčno resinhronizacijsko zdravljenje (CRT) rešujejo življenja pri številnih boleznih srca. Okužba, povezana z napravo, je eden najresnejših zapletov zdravljenja s srčno vsadljivo elektronsko napravo (CIED). Povezan je s precejšnjo obolevnostjo, umrljivostjo in finančnim bremenom zdravstvenega sistema. Stopnja okužbe z elektronskimi napravami za vsaditev srca je nižja v prospektivnih študijah (1,2 %) kot v retrospektivnih registrih (3,4 %).

Dejavniki tveganja za okužbo s CIED

Dejavniki, povezani z bolnikom

Vključujejo: končno ledvično odpoved (ESRD), sladkorno bolezen, mlajšo starost, predhodno okužbo z napravo, podhranjenost, napredovalo stopnjo srčnega popuščanja in zvišano telesno temperaturo pred posegom.

Dejavniki, povezani z vstavitvijo CIED

Vključujejo: pooperativni hematom, dislokacijo elektrode, trajanje postopka, vstavitev naprave CRT (srčna resinhronizacijska terapija), ponovno operacijo in izkušnje operaterja.

Dejavniki, povezani z CIED napravo:

Vključujejo število vstavljenih elektrod in kompleksnost naprave (CRT-D ima največjo).

Preprečevanje:

Pred vstavitvijo: poleg prepoznavanja dejavnikov tveganja, omenjenih zgoraj, opredeljenih za vsakega bolnika posebej, je potrebno upoštevati potencialno korist srčnega spodbujevalnika brez elektrode ali podkožnega implantabilnega kardioverterja-defibrilatorja (ICD). Uporaba teh CIED zmanjša tveganje za okužbo. Profilaktični antibiotiki morajo zajemati vsaj vrsto bakterije Staphylococcus aureus.

Ob vstavitvi CIED: premostitvi antikoagulantnega zdravljenja s heparinskimi zdravili se izognemo, le izjemoma jih uporabimo. Izpiranje žepa z antibiotikom ni priporočljivo (raziskava PADIT). Bolnikom z visokim tveganjem, takimi, kot so bili vključeni v študijo WRAP-IT, lahko koristi antibakterijska mrežasta ovojnica okoli generatorja.

Po vstavitvi: pooperativnega odmerka antibiotike ne priporočamo.

Diagnoza okužbe CIED in s tem povezanih zapletov:
Merila okužbe CIED 2019 za diagnozo okužbe CIED: otekanje žepa generatorja, eritem, toploto, bolečino in gnojni izcedek/tvorbo sinusa ali deformacijo žepa, adherenco in ogroženo erozijo ali izpostavljenost generatorja ali proksimalnih elektrod.

Za odkrivanje vegetacije se lahko uporabi transezofagealna ehokardiografij in/ali intrakardialna ehokardiografija. Pozitronska emisijska tomografija in računalniška tomografija lahko prepoznata nenormalno vnetno aktivnost v žepu ali vzdolž elektrod, ki nakazuje okužbo CIED: lahko jo odkrijemo s (18F)FDG PET/CT skeniranjem ali scintigrafijo z radioaktivno označenim levkociti ali CT s kontrastom. Te preiskave so priporočene pri sumu na infektivni endokarditis, povezanim s CIED, pozitivnih hemokulturah in negativni ehokardiografiji. Rezultati žepnih ali kultur, odvzetih s CIED ali elektrod sovrednostimo kot »minor« mikrobiološka merila.

Zdravljenje okužb s CIED:
Za uspešno zdravljenje dokončne okužbe s CIED je potrebna njihova popolna odstranitev. Sama ekstrakcija se mora izvesti čimprej, brez časovnega zamika po diagnozi okužbe s CIED, saj če se izvede v prvih 3 dneh po hospitalizaciji, to znatno zniža umrljivost v bolnišnici in krajše hospitalizacije. Samo antibiotično zdravljenje lahko poveča 30-dnevno umrljivost za nekajkrat (ne vključuje okužbe površinskega reza, ki zahteva samo antibiotike).
Izolirano okužbo žepa je treba zdraviti z antibiotiki 14 dni pred novo implantacijo, medtem ko sistemske okužbe zahtevajo 4-6 tednov jemanja antibiotikov.

Priporočila, s katerimi je možno preprečiti okužbo po implantacijah CIED, ponovnih implantacijah in alternativnih novih napravah:
Antibiotične profilakse ne priporočamo pred posegi na zobeh, dihalih, prebavilih, genitourinarnem področju ali nekaterimi posegi na srcu (koronarografija, PCI).
Brezelektrodni srčni spodbujevalnik in podkožni ICD sta alternativna oblika CIED pri bolnikih z visokim tveganjem.
Nosljivi (wearable) kardioverter defibrilator je lahko most do ponovne implantacije pri bolnikih z ICD.
Telemedicina ponuja možnosti za preglede rezov na daljavo.

Prognoza, izhodi in zapleti okužb s CIED:
30-dnevna umrljivost zaradi okužbe s CIED je 5-8 %. Večje tveganje napovedujejo dejavniki: ženski spol, endokarditis in končna ledvična odpoved.
Uspešno zdravljeni bolniki imajo podobno prognozo kot tisti, ki nikoli niso bili okuženi.

Minimalne zahteve glede kakovosti ustanove, kjer se vstavljajo CIED, potrebne izkušnje in število vstavitev posameznega operaterja:
Obstaja obratno sorazmerje med izkušnjami operaterja in stopnjo okužbe.
Operaterje z < 100 skupnimi postopki je treba nadzorovati.
Na operaterja se priporoča letni obseg ≥50 vstavitev CIED.

Zaključek

Število implantacij CIED v državah Evropske unije narašča vsako leto, medtem ko se odstotek okužb ne zmanjšuje. S popolnim upoštevanjem smernic in priporočil s tega področja lahko bistveno znižamo odstotek okužb in tako izboljšamo življenje in preživetje bolnikov z vstavljenim CIED.

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INDICATIONS FOR PACING LEAD EXTRACTION AND OVERVIEW OF THE METHODOLOGY

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Introduction

Extraction of cardiovascular implantable electronic devices (CIED) is nowadays a routinely performed and standardized surgical procedure, yet it may be extremely challenging especially in older patient population, in polymorbid individuals and in patients with longer (>10 years) lead's dwell time. Although several different extraction strategies, including simple traction, open heart surgery and transvenous lead extraction (TLE) techniques have evolved, TLE currently represents the cornerstone of CIED extraction, providing a complete, safe and highly effective minimally invasive mode of electronic system removal, especially in the hands of experienced and dedicated health care teams (*1,2*).

Lead extraction techniques

Expanded indications for implantable cardioverter defibrillator (ICD)-, cardiac resynchronization (CRT)- and permanent pacemaker (PM)- therapy over the last 2 decades have led to a significant increase in the use of CIED and, consequently, to a likewise increment in the frequency of CIED-related complications, such as device or lead infections, malfunctions or recalls (*1*). Because a meaningful percentage of CIED-related adverse events demand complete removal of the system from the body, the requirements for CIED extraction have grown significantly in the last 10 years, becoming today one of the most decisive segments in CIED-related care of cardiac patients (*1,2*).

TLE is currently considered the first-line surgical strategy for management of CIED-related adverse events in the majority of patients with chronically implanted devices, regardless of the etiology of the adverse events or the level of evidence for the extraction of the electronic system (*3-5*). Several different technical solutions, ranging from mechanical dilator sheaths and femoral snares to powered traction tools including laser sheaths, hand-powered rotational threaded tip sheaths and electrosurgical dissection sheaths, are available nowadays, showing themselves to be safe, effective and reliable extraction tools in selected clinical scenarios (*3-5*).

Laser sheaths, such as the Spectranetics Laser Sheath II™ (Spectranetics, Colorado Springs, CO USA), deliver cool cutting laser energy to the distal end of the sheath, allowing for cutting of the surrounding tissue without damaging the veins or the insulation of the lead (*5*). Although lead extraction using laser sheaths is an established method with abundant positive data, especially in high-volume centers, evidence indicates that the mortality rates associated with this extremely costly strategy are up to 10 times higher than those associated with mechanical rotational sheaths (*5*).

In recent years, Evolution® RL (Cook Medical, Bloomington, IN USA), a novel type of hand-powered rotational sheath that enables bidirectional rotation, possesses a newly designed and less traumatic

sheath tip and exists in 2 different lengths (with the short version also being stiffer), has been introduced (*5*). Promising results regarding device safety and efficacy have been recently reported by dedicated high- and low-volume centers (*1-5*).

Indications for leads extraction

Indications for lead extraction are summarized in Table 1.

Table 1: Indications for transvenous lead extraction and class of recommendation

INDICATIONS FOR TLE	CLASS OF RECOMMENDATION
NON-INFECTIOUS	
Thrombosis and vascular	
Clinically significant thromboembolic event due to a thrombus on the lead or lead fragment	I
SVC stenosis preventing placement of additional leads	I
Planned stent deployment in a vein already containing a lead to prevent entrapment	I
Symptomatic pacemaker induced SVC syndrome	I
Patients with ipsilateral venous occlusion who require additional leads	IIa
Chronic pain	
Severe chronic pain at device/lead insertion site not managed by medical or other surgical techniques	IIa
Functional leads	
Life-threatening arrhythmias secondary to retained leads	I
Leads interfering with tumor treatment, e.g. in the path of radiation beam therapy	IIa
Abandoned leads interfering with device function	IIa
If CIED implantation would require more than 4 leads on one side or 5 through SVC	IIa
Removal to facilitate MRI imaging with no other alternative	IIb
Lead safety alert/manufacturer recall due to potential for patient harm or early failure	IIb
INFECTIOUS	
Confirmed infection (valvular endocarditis, lead endocarditis or sepsis)	I
Device erosion, pocket abscess or skin adherence	I
Valvular endocarditis without lead/device involvement	I
Gram-positive bacteremia (non-contaminant)	I
Gram-negative bacteremia (persistent)	IIa

Take-home message

A stepwise extraction strategy using a standardized extraction tool by a skilled operator provides the optimal scheme with superior results and an excellent ratio between clinical and/or procedural success and procedure-related complications including high risk sub-populations, such as older patients, individuals with several co-morbidities and patients with very long lead's dwell times.

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ANTIKOAGULANTNA IN ANTITROMBOTIČNA TERAPIJA PRI ARITMIJAH

ANTITHROMBOTIC AND ANTICOAGULATION THERAPY IN THE SCOPE OF ARRHYTHMIA MANAGEMENT

KRATKOTRAJNI ZAGONI ATRIJSKE FIBRILACIJE/ TAHIKARDIJE IN TVEGANJE TROMBEMBOLIČNIH ZAPLETOV

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Uvod

Atrijska fibrilacija (AF) je pomemben vzrok kardioembolične možganske kapi in srčno-žilnih dogodkov. Možganska kap je lahko tudi prva manifestacija AF. Zato ima detekcija AF ima pomembno vlogo pri prognozi. CHA2DS2VASc točkovnik je pomembno orodje za oceno tveganja za možgansko kap in posledično odločitve glede antikoagulacijskega zdravljenja pri bolnikih z AF.

Kljub raziskavam, ki so odkrile številne vzroke možganske kapi, sta najpogostejši vzrok ishemične možganske kapi AF in atrijska undulacija (angl. Atrial flutter, AFL). Približno 25-30 % možganskih kapi pa ostane nepojasnjenih in jih označimo kot kriptogene možganske kapi. Nezaznana AF je lahko del tega fenomena, saj je AF lahko asimptomatska, lahko je kratkotrajna, lahko se prisotne tudi le kratke epizode AF. Nekatere študije predlagajo tudi druge možne vzroke, kot so povečana atrijska ektopična aktivnost (angl. Excessive supraventricular ectopic activity, ESVEA) in kratki zagoni 20 - 50 prezgodnjih atrijskih kontrakcij (angl. Premature atrial contractions, PAC).

Vsebina

Kratke epizode atrijske tahikradije (AT)so pogosta najdba pri snemanju 24- urnega EKG. Povezane so lahko z remodelacijo atrijev in pojavom AF. Vzadnjih letih so dokazali, da je povečana atrijska ektopična aktivnost (angl. Excessive supraventricular ectopic activity, ESVEA) povezana z večjim tveganjem za pojav AF. Prav tako so študije pokazale povečano tveganje za možgansko kap pri bolnikih starejših od 65 let in ESVEA neodvisno od pojava oz. detekcije AF. Prav tako so pokazali, da z naraščanjem CHA2DS2VASc točkovnika narašča tudi tveganje za možgansko kap. Pokazalo se je, da je tveganje za možgansko kap pri bolnikih starejših od 65 let, ki imajo ESVEA in CHA2DS2VASc ≥ 2 približno enako kot pri bolnikih z AF in CHA2Ds2VASc >2. Patofizioloških mehanizmi zaradi katerih je atrijska ektopija (AE) povezana z povečanim tveganjem niso jasni. Najverjetneje pa je povezana z nediagnosticirano AF in tako povečanim tveganjem za možgansko kap. AE je lahko tudi pokazatelj arterijske hipertenzije (AH), sladkorne bolezni (SB), fizične neaktivnosti ali metabolizma lipidov in tako pokazatelj povečanega žilnega tveganja in večjega tveganja za možgansko kap pri takih bolnikih. Tretja, hipotetična možnost je, da obstaja povezava med dejavniki tveganja, kot so AH in kajenje, ki v primeru povečane AE vodijo v dilatacijo levega atrija, stazo v avrikuli levega atrija, fibrozo in endotelijsko disfunkcijo, ki rezultira v hiperkoagulabilnem stanju podobnim kot pri AF.

Detekcija kratkotrajnih zagonov AF/AT je lahko začetek kontinuuma v razvoju AF, saj pri se pri 1 od 5-6 bolikov z AHRE/subklinično AF v 2,5 letih razvije klinična AF. Zato je pri bolnikih starejših od 65 let in

bolnikih z visokim tveganem za možgansko kap smiselno natačnejše monitoriranje z namenom detekcje AF in tako čimprejšnje uvedbe oralnih antikoagulantov. Glede na dosedanje podatke in tudi smernice rutinska uporaba oralnih antikoagulantov zaenkrat še ni svetovana pri kratkotrajnih zagonih AF ali AT. Je pa pri bolnikih s visokim tveganjem za možgansko kap (≥2 točki po CHA2DS2VASc točkovniku) in predvsem pri bolnikih po preboleli možganski kapi uvedba oralnih antikoagulatnov smiselna.

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MANAGEMENT OF ANTICOAGULATION TREATMENT BEFORE CARDIAC PACING DEVICE IMPLANTATION

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Introduction

The use of oral anticoagulation therapy is common among patients undergoing cardiac pacing device implantation, due to their comorbidities such as atrial fibrillation. For many years, discontinuation of oral anticoagulation was required because of the fear of periprocedural bleeding, while heparin bridging was used in hopes of lowering the thromboembolic complications. In the last decade the use of direct oral anticoagulants (DOAC) has become prevalent, mostly due to their safety, ease of use and predictable pharmacokinetics. Regardless, the fear of periprocedural bleeding has not subsided, and inappropriate use of heparin bridging during DOAC discontinuation is still common.

Contents

Cardiac pacing device implantation confers a bleeding risk that ranges from pocket hematoma to cardiac tamponade. The latter is rare, but the incidence of clinically significant pocket haematoma (CSPH) can range between 0.2% and 16.0%, with an average incidence of 4%. CSPH is associated with patient discomfort, sevenfold increased risk of infection, need for reintervention for haematoma evacuation and it increases costs and lengthens hospital stay. Bleeding should be avoided by good surgical technique with minimal tissue trauma and with meticulous attention paid to haemostasis and optimal perioperative management of anticoagulation. For years discontinuation of oral anticoagulant drugs and heparin bridging was the needed, until studies such as BRUISE CONTROL demonstrated that perioperative warfarin continuation reduced CSPH by 80% compared with heparin bridging (3.5% versus 16%). Importantly, there was no difference in the thromboembolic risk between the continued warfarin versus heparin bridging groups. BRUISE-CONTROL-2 trial observed a similarly low risk of hematomas when comparing continued versus interrupted DOAC (2.1% in both groups). No difference in hematomas or thromboembolic risk was found between DOAC versus continued warfarin.

When considering the optimal anticoagulant perioperative management, one should always consider the bleeding risk on one side and the risk of thromboembolic complications on the other. The cardiac pacing device implantation procedure is considered a low bleeding risk procedure, but the bleeding risk can increase in elderly patients, patients with kidney failure, low body weight or concomitant antiplatelet therapy. Also, procedure related bleeding risk tends to be higher in more complex devices and upgrades than de novo implantations. On the other hand, the thromboembolic risk in patients with atrial fibrillation (AF) can be assessed using validated clinical scores, such as the CHA2DS2VASc score, keeping in mind that the postoperative state somewhat increases the thrombotic risk. In patients that take anticoagulant drugs because of venous thromboembolism (VTE) time since the onset of the disease is the most relevant factor when assessing residual thromboembolic risk, while

concomitant persistent risk factors, such as severe thrombophilia or cancer should also be considered.

In patients with low thromboembolic risk perioperative interruption of anticoagulation is an option, otherwise continuation of anticoagulation is preferred. In table 1 a practical advice on perioperative management of anticoagulants before cardiac pacing device implantation is given.

Table 1: Perioperative management of anticoagulants before cardiac pacing device implantation

Patient/procedure characteristics	VKA	DOAC
Low bleeding risk and low thromboembolic risk #	Continue	Short interruption based on type of DOAC and CrCl without heparin bridging
Low bleeding risk and high thromboembolic risk	Continue	Continue or short interruption based on type of DOAC and CrCl without heparin bridging
High bleeding risk * and low thromboembolic risk #	Continue or consider interrupting without heparin bridging	Short interruption based on type of DOAC and CrCl without heparin bridging
High bleeding risk * and high thromboembolic risk	Continue	Continue or short interruption based on type of DOAC and CrCl without heparin bridging

VKA – vitamin K antagonists; DOAC – direct oral anticoagulants; CrCl – creatinine clearance
*high bleeding risk: patient: elderly patient, low body weight, renal failure, concomitant antiplatelet therapy, device upgrade, generator replacement, lead extraction
low thromboembolic risk: nonvalvular AF with CHA2DS2VASc≤4 (no prior stroke or TIA), VTE > 12 months ago, bileaflet AVR *without* major risk factors for stroke

Take-home message

Cardiac pacing device implantation is considered to be a low bleeding risk procedure. In most patients, the procedure can be safely performed on continued oral anticoagulation, however a short discontinuation without heparin bridging might be considered in patients with a higher bleeding risk and low thromboembolic risk. Patient's characteristics and surgical factors should be considered in managing anticoagulation therapy preoperatively.

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MANAGEMENT OF PERIPROCEDURAL ANTICOAGULATION TREATMENT IN CATHETER ABLATION OF ARRHYTHMIAS

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Introduction

During the past two decades, radiofrequency catheter ablation (RFA) has become widely accepted and successful modality for treatment of various types of arrhythmias. At the same time, electrophysiologists frequently perform more invasive procedures, increasingly involving the left chambers of the heart. During the procedure a risk of thromboembolic complications, and bleeding complications both exist, and need to be considered. Due to the invasive nature of the procedure, there is inherent risk of bleeding complications at vascular access sites, as well as in case of damage to the myocardial wall due to the catheter manipulation, or excessive radiofrequency energy application. On the other side, a small but existing risk of periprocediral and postprocedural thromboembolism stems from patient's comorbidities, and activation of procoagulant activity by endothelial damage caused by RFA. With appropriate systemic anticoagulation we can minimize the risk of systemic embolization, but need to be balanced with the concurrent bleeding risks. Both risks vary widely among different types of arrhythmias and procedures, and pre- and intraprocedural anticoagulation needs to be adjusted, accordinglly.

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Catheter ablation in the right heart chambers (except atrial flutter)

As a rule, RFA in the right heart chambers is not associated with increased risk of systemic thromboembolism, unless there is significant right to left shunt. Consecutively, aggressive systemic anticoagulation is not needed. To prevent deep vein thrombosis, which was reported in up to 5 % of cases, especially in prolonged procedures, and to prevent formation of thrombus at the end of vascular sheath, a single bolus of unfractionated Heparine (2500 – 5000 IE) is applied at the start of procedure.

Should patients require oral anticoagulation or platelet inhibition for another reason, iscontinuation of these agents before the ablation procedure is not mandatory. For patients with planned right ventricular ablation, it might be rasonable to omit the morning dose of anticoagulant on the day of procedure, or aim for INR between 2 and 2,5 in case of warfarine.

Catheter ablation in the left atrium (and typical atrial flutter)

Ablation in the left atrium increases thromboembolic risk due to the introduction and manipulation of catheters and long sheaths into the left atrium, and also due to endocardial lesions produced during RFA. Cerebral imaging studies have shown micro embolic events post-ablation, however clinical relevance of such is currently unclear. So far, there was no clear correlation with clinical overt cognitive

deficits. In addition, some arrhythmuias originating in the left atriumj, as well as right sided atrial flutter carry intrinsic thromboembolic risks. Management of anticoagulation, therefore, differs based on the underlying arrhythmia mechanism.

- Left sided accessory pathway, and focal atrial tachycardia do not carry intrinsic arrhythmia associated thrombembolic risk and long term anticoagulation is not needed. Procedure related thrombembolic risk is mitigated by unfractionated heparine administration, with target ACT of > 300 s. Postprocedurally, no anticoagulation, or aspirine is recommended due to lack of evidence that such strategies provide any benefit. However, in case of prolonged procedure, with higher number of RFA lessions, aspirine might be considered for 4 to 6 weeks postprocedurally.
- Atrial fibrillation, left and right atrial flutters carry both intrinsic, and procedure related risks predisposing to thrombembolism, as stated before. As a rule, periprocedural anticoagulant management is the same for all of these patients. In anticoagulation naive patients, initiating therapeutic anticoagulation 3 - 4 weeks before ablation is desirable. With respect to the periprocedural anticoagulant management in patients undergoing AF ablation, current guidelines recommend performing the ablation under uninterrupted warfarine or direct oral anticoagulant (DOAC) treatment, provided the INR is within therapeutic range. Furthermore, DOAC seems to be preferred anticoagulant based on the observations from several studies and meta-analyses comparing uninterrupted warfarine vs. DOAC strategies. These showed similar rates of stroke/TIA, or silent cerebral embolic events post-procedurally, with significantly lower incidence of bleeding with the use of uninterrupted DOAC strategies. In all studies, DOACs were used truly uninterrupted, and this indicates that there is no reason to omit one or two DOAC doses before the procedure. First dose after the procedure is typically administered on the evening, provided uncomplicated procedural course. Oral anticoagulation should be continued for at least 2 months after ablation, since there is evidence that the vast majority of thromboembolic events occurs in the first 4 weeks after ablation. After that, per current guidelines, continuation of oral anticoagulation is based on the thromboembolic risk assessment by clinical scores. Recently, accumulating data indicates, that after successful RFA of AF, thrombembolic risk is modified, such that low, and even moderate risk groups of patients, did not show excess of thromboembolic events when warfarin was discontinued, compared to those kept on warfarin. At the same time, rate of bleeding was significantly reduced. Whether these results will extend to the DOAC strategies, is unclear.

Catheter ablation in the left ventricle

In contrast to RFA of AF, there is much less evidence from well controlled trials regarding the most appropriate anticoagulation strategies in patient undergoing ventricular tachycardia (VT) ablation in the left ventricle (LV). It is known that there is about 1 % risk of periprocedural stroke even in VT ablation and therefore periprocedural anticoagulation is warranted. On the other side, VT ablation is sometime associated with arterial vascular access, or pericardial space access for epicardial ablation. Those approaches are regarded as riskier for potential bleeding complications and warrant consideration in the context of periprocedural anticoagulation management.

Pre-procedural anticoagulation is not required unless otherwise indicated in patients without structural heart disease. There is consensus that, in patients on a warfarin and a therapeutic INR,

anticoagulant should not be interrupted for VT ablation, unless epicardial access is planned. When on DOAC, it is recommended to stop the drug 24 hours before the procedure, although this recommendation is based on 5 years old document.

Intra-procedurally, therapeutic intravenous heparin is recommended in patients with and without structural heart disease, with target ACT of 300s. When pericardial space access is planned, full dose of heparin is administered once this is achieved.

Regarding post-procedural anticoagulation, there are little well-controlled studies, and recommendations are based on consensus documents. After less extensive ablation, and especially in the absence of structural heart disease, a 4 to 6 week of antiplatelet drug is recommended. It showed equal efficacy as oral anticoagulant in preventing thromboembolic events in one study. After more extensive ablation, and especially in the setting of significantly depressed LV systolic function, most experts consider institution of oral anticoagulant for 4 to 12 weeks. This recommendation has been corroborated by data from two recent studies. In the first, a significant coagulation cascade activation was documented following endocardial RFA of VT in the LV. This response was suppressed with oral anticoagulation, which indicates potential preventive effect versus periprocedural thromboembolic events. Second clinical study compared two strategies with aspirin and DOAC following RFA in the LV. Patients treated with DOAC had reduced risk of stroke/TIA, and silent cerebral micro-emboli following catheter ablation in the LV, compared to aspirin. Therefore, it seems, that treatment with DOAC for a limited period of time is reasonable following RFA in the LV.

Take-home message

Catheter ablation of arrhythmias in right sided heart chambers is generally not associated with increased thrombembolic risk, therefore, periprocedural anticoagulation is not needed. Catheter ablation in the left atrium and ventricle is associated with increased risk of thromboembolic events. Procedures in the left atrium are performed under uninterrupted anticoagulation. Based on recent data, oral anticoagulation with DOAC for a limited period of time is reasonable following catheter ablation in the LV.

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NOVOSTI V OBRAVNAVI BOLNIKA Z GENETSKO KARDIOMIOPATIJO

MANAGEMENT OF PATIENT WITH GENETIC CARDIOMYOPATHY

CARDIAC IMAGING MODALITIES IN THE DIAGNOSTIC WORKUP OF PATIENT WITH GENETIC CARDIOMYOPATHY

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Introduction

The current classification of cardiomyopathies, proposed in 2008 by the European society of cardiology (ESC) working group on myocardial and pericardial diseases, differs 4 morphological and functional phenotypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). Cardiomyopathies that cannot be grouped in these 4 phenotypes are labeled "unclassified". Each group consists of several genetic and non-genetic diseases. The following abstract will focus on the role of multimodality cardiac imaging in the diagnosis of HCM, DCM and ARVC.

Hypertrophic cardiomyopathy

In an adult, HCM is defined by left ventricular (LV) wall thickness ≥15 mm in one or more myocardial segments as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography (CT))—that is not explained solely by loading conditions. In up to 60% the disease is caused by mutations in cardiac sarcomere protein genes. Other etiologies include infiltrative diseases (amyloidosis), metabolic disorders (e.g. Anderson-Fabry disease), mitochondrial, neuromuscular diseases and others. Echocardiography is the first-line imaging technique, crucial in establishing the degree and the pattern of LV hypertrophy, LV systolic and diastolic function, LV outflow tract obstruction, abnormalities of the mitral valve and other cardiac structures. A number of echocardiographic features can point to specific diagnosis, like asymmetric septal hypertrophy to sarcomeric HCM, concentric hypertrophy with pericardial effusion and thickened interatrial septum to cardiac amyloidosis etc. CMR offers incremental value in patients with LV hypertrophy and should be according to the ESC guidelines performed at baseline assessment if local resources and expertise permit. CMR is particularly useful to detect apical and lateral LV wall hypertrophy, aneurysms, thrombi, to assess right ventricle (RV) and subtle markers of HCM like myocardial crypts and papillary muscle abnormalities. By detecting myocardial fibrosis, both focal replacement fibrosis with late gadolinium enhancement (LGE) and diffuse interstitial fibrosis with T1 mapping techniques, CMR adds important diagnostic and prognostic information. Patchy mid-wall pattern of LGE in the areas of LV hypertrophy is typical for sarcomeric HCM and conveys important risk for sudden cardiac death. In cardiac amyloidosis, there is often global diffuse LGE with similar myocardial and blood-pool gadolinium kinetics and very high native T1 values. On the other hand, Anderson-Fabry disease is characterized by a reduction in native T1 values (due to lipid accumulation) and the presence of posterolateral LGE. Cardiac CT usually serves as a third-line imaging modality in HCM, when echocardiography and CMR are not available or contraindicated. The major clinical contribution of nuclear imaging is in detection of transthyretin amyloidosis.

Dilated cardiomyopathy

DCM is defined by the presence of LV or biventricular systolic dysfunction with or without dilatation in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment. The underlying etiologies include genetic (with a growing number of identified genes), inflammatory (chronic myocarditis, autoimmune diseases), toxic, drug-induced, metabolic and other causes. Comprehensive echocardiography is mandatory to asses global ventricular anatomy and function, dyssynchrony and hemodynamics. LV strain imaging is important to assess subtle systolic dysfunction associated with early phenotypes. CMR is important to consider (at least once) in every patient with DCM. The presence and pattern of LGE is of paramount importance to exclude ischemic etiology. About one third of DCM patients show linear mid-wall LGE, which is a strong independent predictor of adverse outcome. Higher T1 values, reflecting diffuse myocardial fibrosis, are characteristic and may be used for detection of early stages of the disease. Higher T2 values reflecting myocardial edema and inflammation have been shown to discriminate between chronic myocarditis and non-inflammatory causes of DCM. On the other hand, shortened native T1 and T2* times are pathognomonic for hemochromatosis. The role of cardiac CT and nuclear imaging techniques is primarily in excluding significant coronary artery disease.

Arrhythmogenic (right ventricular) cardiomyopathy

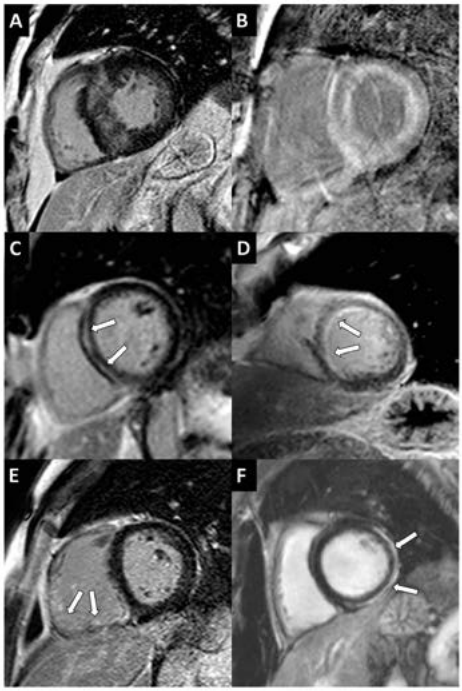
ARVC is a genetically determined heart muscle disease characterized by progressive fibrofatty replacement of the RV myocardium which may act as a substrate for ventricular arrhythmias and sudden cardiac death. Biventricular and left-dominant disease variants have been identified, therefore the new term "arrhythmogenic cardiomyopathy" may better reflect the broader spectrum of the disease. Global and regional RV dysfunction is one of the main diagnostic criteria for the ARVC (which currently do not include the LV dominant and isolated LV disease). Echocardiography is indicated in the initial evaluation of a patients, however CMR due to its potential to detect subtle functional and structural RV wall abnormalities as well as myocardial fibrofatty replacement has evolved into a gold standard for the assessment of patients with suspected ARVC. In addition, the presence of subepicardial or mid-myocardial LGE affecting multiple LV segments (most commonly the inferolateral wall) may reveal concomitant or isolated LV disease. Low native T1 values and fat-saturation sequences can detect areas of fibrofatty replacement and may obviate the need for endomyocardial biopsy.

Take-home message

Multimodality cardiac imaging plays a key role in the diagnosis and prognosis of patients with cardiomyopathies. Echocardiography is the first line imaging technique and is complemented by the CMR. Myocardial tissue characterization has revolutionized the diagnostic capabilities of different cardiomyopathy phenotypes.

A core Image: LGE CMR in the diagnostic workup of cardiomyopathies. Panels A and B show the examples of the HCM phenotype, panels C and D of the DCM phenotype and panels E and F of the ARVC phenotype. **(A)** Patchy mid-wall LV myocardial enhancement in the areas of maximum LV thickness is characteristic for sarcomeric HCM (present in 33–84% of patients). **(B)** Global diffuse LGE with similar

myocardial and blood pool signal intensity is typical for cardiac amyloidosis. **(C)** Linear mid-wall LGE in the interventricular septum (white arrows) occurs in about one third of DCM patients. It is specific for a non-ischemic cardiomyopathy, but does not allow differentiation between DCM subtypes. **(D)** Subendocardial LGE in a coronary artery perfusion territory (the LAD perfusion territory in the Figure, white arrows) is specific for ischemic cause of cardiomyopathy. **(E)** ARVC may present with isolated LGE of the RV (white arrows). RV dilatation is evident as well. **(F)** The presence of extensive subepicardial or mid-myocardial LGE affecting multiple LV segments (inferior and lateral wall in the Figure, white arrows) may suggest left-sided ARVC.



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SUDDEN CARDIAC DEATH RISK STRATIFICATION IN PATIENTS WITH GENETIC CARDIOMYOPATHY

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Introduction

Classic cardiomyopathy classification according to phenotypes differs between dilated (DCM), hypertrophic (HCM), restrictive and arrhythmogenic right ventricular cardiomyopathies (ARVC). With broader availability of genetic testing and the rapid progress of cardio genetics, it is increasingly recognised that phenotypes may overlap and genotyping enables better risk stratification and prognostic value.

Contents

Sudden cardiac death (SCD) risk in patients with DCM has decreased substantially with the increasing use of evidence-based heart failure medical therapy. The recommendation for primary prevention implantable cardioverter defibrillator (ICD) implantation in symptomatic patients with DCM has therefore been downgraded from I to IIa in the 2022 ESC Guidelines with left ventricular ejection fraction (LVEF) below 35% as a sole risk discriminator. However, in recent years myocardial fibrosis, detected by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR), has emerged as a strong predictor of ventricular arrhythmias (VA) and SCD. Pathogenic variants in certain genes like LMNA, FLNC, PLN, and RBM20 have consistently been associated with higher rates of VA and SCD. Additional risk stratification besides LVEF is thus recommended. Genetic testing is recommended in all DCM patients and patients with hypokinetic non-dilated cardiomyopathy (HNDCM) younger than 50 years with either positive family history or AV conduction disorder. CMR should be considered in all DCM/HNDCM patients. Sudden cardiac death risk is considered high even in patients with mildly reduced ejection fraction (LVEF<50%) and two or more of the following risk factors: syncope, LGE on CMR, pathogenic variants in genes LMNA, FLNC, PLN, or RBM20 and inducible sustained monomorphic ventricular tachycardia (SMVT) at programmed electrostimulation (PES). ICD implantation in these patients should be considered. A risk calculator has been developed for patients with a pathogenic variant in the LMNA gene, which is available online at https://lmna-risk-vta.fr.

ARVC is characterised by fibrofatty myocardial replacement of the right ventricular myocardium. The disease is caused by pathogenic variants in desmosomal and, less commonly, non-desmosomal genes. Wider use of CMR, genetic testing and phenotyping of large patient cohorts revealed a broader disease spectrum in which both ventricles can be involved. Since the phenotypical overlap with DCM is common, the term "arrhythmogenic cardiomyopathy" has been proposed in a group of disorders in which ventricular arrhythmia and the dysfunction of one or both ventricles are the defining features. Primary prevention of SCD with an ICD implantation should be considered in patients with ARVC and severe RV or LV systolic dysfunction or patients with moderate RV or LV systolic dysfunction and either non-sustained ventricular tachycardia (NSVT) or SMVT at PES.

HCM is defined by increased LV wall thickness not explained by abnormal loading conditions. An autosomal dominant sarcomeric gene mutation usually causes it. VA and SCD risk mainly depend on age and risk profile. A risk calculator HCM Risk-SCD is available at https://doc2do.com/hcm/webHCM.html for 5-year risk of SCD calculation. Additional risk factors not included in the risk calculator are LVEF < 50%, apical aneurysm, extensive LGE on CMR (≥15% of LV mass), abnormal blood pressure response during exercise test and the presence of a sarcomeric mutation. Primary SCD prevention with an ICD implantation should be considered in all patients with a high estimated risk (≥6% in 5 years) or those with moderate risk and one or more additional risk factors.

A core Table

Risk stratification and primary SCD prevention (adapted from the 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death)

DCM	ARVC	HCM
Diagnostic evaluation/risk stratification		
CMR and genetic testing in patients < 50 years and with positive family history or AV conduction delay	CMR and genetic testing	CMR and genetic testing
General measures		
Guideline-directed medical therapy (GDMT)	Avoidance of high-intensity exercise Beta blocker may be considered	
ICD implantation for primary SCD prevention (all class of recommendation IIa)		
DCM/HNDCM with symptomatic heart failure and LVEF ≤ 35% despite GDMT	Severe RV or LV systolic dysfunction	Estimated 5-year risk of SCD ≥ 6%
DCM/ HNDCM, LVEF < 50% and ≥2 risk factors (syncope, LGE on CMR, inducible SMVT at PES, pathogenic mutations in LMNA, PLN, FLNC, and RBM20 genes).	Moderate RV or LV dysfunction, and NSVT or inducibility of SMVT at PES	5-year risk of SCD 4 -6% and with either significant LGE at CMR (≥15% of LV mass); LVEF <50%; abnormal blood pressure response during exercise test; LV apical aneurysm; presence of sarcomeric pathogenic mutation
DCM/ HNDCM with a pathogenic mutation in LMNA gene, 5-year risk of life-threatening VA ≥10% and NSVT or LVEF < 50% or AV conduction delay		

Take-home message

Extensive diagnostic evaluation with broader use of CMR and genetic testing in patients with different cardiomyopathy phenotypes provides better sudden cardiac death risk stratification and therapeutic decision-making.

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KATETRSKA ABLACIJA ARITMIJ PRI GENETSKIH KARDIOMIOPATIJAH

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Uvod

Bolniki s strukturno boleznijo srca (SHD), kot so tudi genetske kardiomiopatije (KMP), so ogroženi v prvi vrsti zaradi prekatnih aritmij (VA) oziroma nenadne smrti. Zato so kandidati za vsaditev kardioverter-defibrilatorja (ICD). Z ICD seveda ne zmanjšamo bremena VA. Zato potrebujejo ti bolniki tudi antiaritmično zdravljenje. Izbor antiaritmičnih zdravil (AAD) je pri bolnikih s SHD omejen zaradi njihovih proaritmičnih učinkov in neugodnih učinkov na srčno funkcijo. Na voljo ostane predvsem amiodaron, ki je toksičen in zaviralci receptorjev beta. Zato je na mestu razmislek o katetrski ablaciji. V zadnjih desetletjih smo se veliko naučili o mehanizmih aritmij. Priča smo hitremu razvoju ablacijskih tehnik in tehnologij. Prve uspešne katetrske ablacije so bile opravljene pri bolnikih s kračno prekatno tahikardijo (VT). Nato smo že uspeli obvladati električni vihar in zmanjšati breme VT pri bolnikih z ishemično KMP. Vse uspešnejša pa je v zadnjih letih tudi katetrska ablacija VT pri genetskih KMP in nekaterih genetskih aritmijah. Mogoča je celo ablacija prekatne fibrilacije/polimorfne VT, sprožene z enako prekatno ekstrasistolo (VES), največkrat iz Purkynějevega nitja. Brazgotina je substrat večine VT, katerih mehanizem je kroženje depolarizacije. Brazgotina leži pri bolnikih z ishemično KMP endokardno in je bolj omejena, kot pri genetskih KMP, kjer je brazgotina difuzna in razporejena v steni ali epikardno. Zato je uspešnost katetrske ablacije VT pri genetskih KMP manjša kot pri ishemični etiologiji. V večjem odstotku je treba opraviti še epikardne ablacije. V razvoju so tudi nove ablacijske tehnike (npr. bipolarna ablacija, alkoholna ablacija, avtonomna modulacija, radioterapija, kirurški pristopi itd.), ki omogočajo boljši ablacijski uspeh pri težjih primerih. Pri načrtovanju katetrske ablacije moramo, poleg zapisa EKG klinične VT ali sprožitvene VES, pridobiti vse slikovne podatke o substratu VT – brazgotini (ultrazvok, magnetna resonance, računalniška tomografija). Povprečni dolgoročni uspeh katetrske ablacije VT pri genetskih KMP je od 30- do 70-odstoten. Najboljši je pri aritmogeni KMP desnega prekata, slabši pa pri dilatacijski KMP. Upoštevati moramo, da so zapleti med ablacijskim posegom lahko zelo resni (možganska kap, tamponada in smrt).

Preddvorna fibrilacija (AF) je del sindroma genetskih KMP, saj doseže visoko prevalenco 30–70 %. O dolgoročni uspešnosti ablacijskega zdravljenja AF je malo podatkov. Boljši uspeh lahko pričakujemo v začetni fazi bolezni, vendar bolezenska slika s časom pogosto napreduje, zato je trajnejši uspeh manj verjeten. Kontrola srčne frekvence (farmakološka, ablacijska) ima verjetno prednost pred radikalnim ablacijskim zdravljenjem. Izjema je morda hipertrofična KMP.

Vsebina

V predavanju bomo predstavili najnovejše indikacije za katetrsko ablacijo VT v sklopu genetskih KMP, kot so: dilatacijska KMP/ ne-dilatacijska hipokinetična KMP, aritmogena KMP desnega ventrikla in hipertrofična KMP. Razpravljali bomo o uspešnosti ablacijskega zdravljenja AF pri genetskih KMP in aritmijah. Omenili bomo indikacije za ablacijsko zdravljenje tudi pri nekaterih primarnih genetskih aritmičnih sindromih in drugih strukturnih boleznih srca.

Ključno sporočilo

Pri izbranem bolniku z genetsko KMP (in aritmijo), ki ima simptomatsko, obstojno, monomorfno VT ali AF z znaki srčnega popuščanja, moramo pomisliti na možnost zdravljenja s katetrsko ablacijo. To velja še posebej takrat, kadar je AAD kontraindicirano, neučinkovito ali ga bolnik ne prenaša. Ker je ablacijski poseg zahteven, zapleti pa lahko resni, napotimo bolnika v specializiran aritmološki center, kjer imajo stalen program ablacijskega zdravljenja VA in AF pri strukturni bolezni srca in vso podporno dejavnost, ki je nujna v primeru resnega zapleta. Tem merilom zadosti trenutno samo aritmološki center v UKC Ljubljana.

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FARMAKOLOŠKO ZDRAVLJENJE BOLNIKOV Z GENETSKO KARDIOMIOPATIJO

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Uvod

Nedavna spoznanja so pokazala, da temeljno patofiziološko izhodišče večine kardiomiopatij predstavljajo mutacije specifičnih genov. Genetske kardiomiopatije razvrščamo v tri večje podskupine, in sicer v hipertrofično kardiomiopatijo (HCM), dilatativno kardiomiopatijo (DKMP) in aritmogeno kardiomiopatijo (AC). Historično smo te diagnoze postavljali s pomočjo uveljavljenih kliničnih, morfoloških in histoloških kriterijev, danes pa v ospredje diagnostike in klasisifikacije teh kardiomiopatij vedno bolj vstopa korelacija genotipa in fenotipa, ki hkrati nudi poglobljen vpogled v njihove kompleksne patofiziološke mehanizme in odpira možnosti specifičnega (tarčnega) zdravljenja.

Genetski vzroki kardiomiopatij

40-50 % bolnikov s HCM je nosilcev mutacije na vsaj enem od osmih genov za sarkomerne proteine, redkeje pa pri tej kohorti bolnikov srečamo tudi mutacije na nesarkomernih genih, kot so CSRP3, FHL1, PLN, FLNC in ALPK3. Izkazalo se je, da se HCM pri bolnikih s prisotno vsaj eno mutacijo v primerjavi z »genotip negativnimi« HCM bolniki pojavi bolj zgodaj, razvije se izrazitejša hipertrofija, zvišano pa imajo tudi tveganje za srčnožilne zaplete (1).

Pri bolnikih z DKMP opredelimo mutacijo pri 20-35 %. Genetska arhitektura pri DKMP je izrazito raznolika, saj vključuje mutacje vseh kompartmentov kardiomiocita (jedrne membrane, sarkomere, Z-diskov, dezmosomov in citoskeleta). To so nato odraža v veliki variabilnosti delovanja kardiomiocitov (kontrakcija, strukturna trdnost, delovanje ionskih kanalčkov, metabolizmu itd.). Analize korelacije genotipa in fenotipa so pokazale, da pri bolnikih z DKMP najpogosteje srečamo mutacije na genih za LMNA, DSP, RBM20 in FLNC (1).

Čeprav AC navadno povezujemo z boleznijo desnega prekata, pa lahko srečamu tudi izolirano prizadetost levega prekata ali, pogosteje, biventrikularno prizadetost. Tipično AC povezujemo z mutacijami v genih dezmosomskih genih (PKP2, JUP, DSG2 in DSC2), redkeje pa bolezen povzezujemo z mutacijami nedezmosomskih genov (TMEM43, PLN in DES) (1).

Pri vseh navedenih podtipih kardiomiopatij je prevladujoč način dedovanja genov avtosomno dominantni, pri vsaki mutaciji pa je pomembno opredeliti ali gre za t.i. »loss-of-function« ali »gain-of-function« mutacijo, saj to ključno določa vpliv, sicer precej variabilni vpliv, teh mutacij na preoblikovanje miokarda in vpliva na možnosti in pristope specifičnega zdravljenja.

Splošni pristop k zdravljenju genetskih kardiomiopatij

Pri bolnikih s DKMP se glede zdravljenja srčnega popuščanja ravnamo po aktualnih smernicah, ki svetujejo štiritirno zdravljenje z neprilizinskimi zaviralci (ali ACEI/ARB), blokatorji receptorjev beta, mineralokortikoidnimi antagonisti in SGLT2 zaviralci ter po potrebi diuretiki. Pomembno je poudariti, da nobena od ključnih študij, ki so utemeljile tovrstno zdravljenje, ni vključevala podatkov o ev. mutacijah. Tako zaenkrat ne vemo, kako prisotnost specifične mutacije vpliva na klinične izhode »klasičnega« zdravljenja srčnega popuščanja. Pri bolnikih s HCM in AC jasnih dokazov o kliničnih koristih štiritirnega zdravljnenja zaenkrat nimamo (2).

Novi pristopi k zdravljenju genetskih kardiomiopatij

Genska nadomestna terapija

Temeljni namen genske nadomestne terapije (ang. gene replaceent therapy, GRT) je trajno nadomestiti neustrezno delujoč gen z normalnim genetskim zapisom. Čeprav ta koncept ni nov, sta v preteklosti glavni omejitvi tovrstnega pristopa predstavljali varnost in učinkovitost vektorske dostave genov v ustrezne celice. Šele nedavno so vekotorje izpopolnili do te mere, da so dovolj učinkoviti in varni, da jih lahko uporabljamo tudi v humani medicini in prvi rezultati pri bolnikih z distrofijo mrežnice in spinalno mišično atrofijo so vzpodbudni (1).

Pri bolnikih z genetskimi kardiomiopatijami bi tovrstni pristop utegnil učinkovati pri bolnikih z »loss-of-function« mutacijo, ki jo pravioma srečamo pri genih, kot so MYBPC3, TTN, LMNA, DSP, PKP2, BAG3 in FLNC. Trenutno je v teku prva klinična študija z GRT pri bolnikih z Danonovo boleznijo, ki je posledica »loss-of-function« mutacije gena za LAMP2 (1).

Predvidevajo tudi da bi GRT ravno tako lahko učinkovala pri bolnikih z »missense« mutacijami, kjer celica proizvaja neustrezen protein. Z vnosom ustreznega gena in s proizvodnjo ustreznega proteina bi lahko preglasili neustrezen protein in s tem upočasnili oz. zavrli bolezenski proces nastanka kardiomiopatije.

Kljub velikemu potencialu in obetajočim rezultatom pa ima danes tehnologija GRT pri zdravljenju kardiomiopatij še nekaj omejitev:

- velikost genskega zapisa (treutno zaradi velikosti vektorja omejena na 4,7 kb)
- trajnost učinka (trenutno se nadomestni geni ne integrirajo v genetski zapis bolnika, kar omejuje trajanje učinka)
- nizka transdukcija (dostava genov v tarčne celice)
- nevtralizacijska protitelesa (zmanjšujejo učinkovitost prve in ponovnih aplikacij)
- neželeni učinki na ne-tarčnih tkivih

Terapija utišanja genov

S terapijo utišanjagenov (ang. gene slinecing therapy, GST) zmanjšujemo ekspresijo mutiranih genov, s tem pa v celici zmanjšujemo prisotnost neustreznih/nedelujočih proteinov. GST deluje na principu interfirajoče RNA, ki na ribosomu prepreči translavijo RNA mutrianega gena. Ta koncept so v predkliničnih čtudijah že potrdili pri genih za MYH6 in MYL2 (1).

Čeprav GST predstavlja zanimiv koncept, pa je ta pristop od rutinske klinične uporabe še precej oddaljen. Ključni omejitvi tega pristopa sta:

- interfirajoča RNA mora biti specifična za vsako mutacijo posebej (problem širše uporabnosti)
- utišanje enega alela lahko vodi v iantrogeno haploinsuficienco (neznan dolgoročni učinek, možna kombinacija GST in GRT)
- neželeni učinki na ne-tarčnih tkivih

V klinični medicini danes poznamo le en primer učinkovite aplikacije GST in sicer pri ATTR amiloidozi, kjer z GST (patisiran) učinkovito utišamo TTR gen in s tem preprečimo nastanek oz. progres polinevropatije. Študija APOLLO-B je nadalje potrdila tudi ugodne klinične učinke patisirana na ATTR kardiomiopatijo (1).

Modifikacija genov

Modifikacijo genov omogoča nedavno razvita tehnologija CRISPR-Cas9, ki temelji na popravi obstoječega genetskega zapisa. Poprava genetskega zapisa samo s CRISPR-Cas9 generira pojav nehomolognega povezovanja koncev, posledica česar so dodatne insercije ali delecije tarčnega mesta, kar navadno povzorči premik bralnega okvirja in s tem prezgodnjo krnitev. Homologno rekombinacijo sicer lahko dosežemo z DNA predlogami. Ključno omejitev CRIPST-Cas9 tehnologije pri zdravljenju genetskih kardiomiopatij trenutno predstavlja zelo nizka stopnja homologne rekombinacije, še posebej v kardiomiocitih in tehnologije, ki bi naslovile to omejitev in omogočale direktno popravo genetskega zapisa z metodo CRIPSR-Cas9 so predmet številnih aktualnih predkliničnih raziskav (1).

Modulacija primarnih patofizioloških zank

Pri genetskih kardiomiopatijah primarne patofiziološke zanke predstavljajo celične procese, ki nastanejo kot neposredna posledica mutacije določenega gena.

a) Direktna modulacija kontraktilnosti

Spremembe kontraktilnosti miokarda v kontekstu kardiomiopatij predstavljajo eno od temeljnih sprememb njegovega delovanja. Medtem ko se pri DKMP navadno srečamo s hipokontraktilnostjo miokarda, imamo pri HCM praviloma opravka z njegovo hiperkontraktilnostjo. Spremembe kontraktilnosti miokarda so pri kardiomiopatijah lahko pomembno pogojene s prisotnimi mutacijami, največkrat proteinov kontraktilnega aparata ali pa citoskeletnih proteinov.

Miozinski modulatorji (omecmtiv mecarbil, danicamtiv) lahko tako pri bolnikih z DKMP preko povečanja aktivnosti miozinske ATPaze povečajo kontraktilnost miokarda ob nespremenjenem metabolizmu Ca2+ (ki se sicer močno spremeni ob klasični inotropni terapiji). Klinična študija z omecamtiv mecarbilom (GALACTIC-HF) sicer ni bila pozitivna in trenutno je mesto miozinskih aktivatorjev v rutinski obravnavi bolnikov z DKMP še nejasno (3). Vsekakor pa hemodimaski podatki kažejo, da z njimi lahko učinkovito kompenziramo zmanjšanje kontraktilnosti miokarda (tudi tiste, nastale neposredo zaradi ev. mutacije).

Pri bolnikih s HMC se je izkazalo, da lahko hiperkontraktilnost moduliramo z zdravilom mavacamten, ki stabilizira miozin v avtoinhibiranem stanju, s tem pomembno zmajša število aktomiozinksih povezav in posledično negatvno (ugodno) vpliva na kontratilnost pri tej populaciji bolnikov. Nedavno objavljena

študija EXPLORER-HCM je pokazala ugodne hemodinamske (zmanjšanje dinamične obstrukcije v LVOT) in klinične učinke mavacamtena pri bolnikih z obstruktivno obliko HCM (4), študija VALOR pa pomembno manjšo potrebo po septotomijah pri tej populaciji bolnikov (5), kar potrjuje ugodne neposredne učinke tega zdravila na miokard. Mavacamten je tako postal prvo specifično zdravilo za bolnike z obstruktivno obliko HCM. Uporabnost tega terapevtskega pristopa pri širši populaciji bolnikov s HCM zaenkrat ostaja še neopredeljena, saj študija MAVERICK-HCM pomembnega hemodinamičnega ali kliničnega izboljšanja pri bolnikih z neobstruktivno HCM, ki so prejemali mavacamten, ni pokazala (6). Odprto ostaja tudi vprašanje, ali kronična terapija z modulatorji miozina vpliva na progres HCM in z njo povezane zaplete. Ravno tako nobena od navedenih študij ni primerjala učinkov mavacamtena glede na genotip bolnikov.

Potencialno tarčno pri modulaciji kontraktilnosti predstavljajo tudi drugi kontraktilni proteini v sarkomeri. Še posebej zanimiva se zdi modulacija občutljivosti troponina na Ca2+, saj bi lahko s tem učinkovito zdravili tako bolnike z DKMP (s povečanjem občutljivosti) in HCM (z zmanjšanjem občutljivosti), so pa vsi podatki zaenkrat omejeni na rezultate in-vitro oz. na živalske modele (1).

Stabilizatorji proteinov

Pri nekaterih kardiomiopatijah ključni patofiziološki proces predstavlja kopičenje kardiotoksičnih proteinov v miokardu. Tipičen predstavnik te skupine so amiloidoze, v zadnjih letih pa je bil največji napredek napravljen pri zdravljenju bolnikov z ATTR amiloidozo. Pri teh bolnikih konformacijska nestabilnost tetramerne oblike transtiretina vodi v nastanek amiloidnih fibril, ki se lahko odlagajo tudi v miokardu. Študija ATTR-ACT je pokazala, da stabilizator transtiretina tafamidis pomembno izboljša preživetje in zmanjša število hospitalizacij zaradi poslabšanja srčnega popuščanja (7), zaradi česar so tafamidis že uvrstili v priporočila obravnave bolnikov s srčnim popuščanjem vsa večja kardiološka združenja.

Podobno patofiziologijo odlaganja neustrezno zloženih proteinov (sicer v manjšem obsegu) srečamo tudi pri nekaterih drugih genetskih kardiomiopatijah (npr. pri mutaciji FLNC). Ali bodo stabilizatorji proteinov pri teh kardiomiopatijah imeli podobne klinične učinke kot pri ATTR kardiomiopatiji pa bodo pokazala prihodnje predklinične in klinične študije.

Ključno sporočilo

Danes vemo, da se za večino primarnih kardiomiopatij skrivajo mutacije genov, ki pomembno spreminjajo strukturo in/ali funkcijo kardiomiocitov. Temeljni pristop k zdravljenju teh bolnikov še vedno predstavlja štiritirna terapija srčnega popuščanja. Nova spoznanja pa prinašajo tudi tarčne možnosti zdravljenja, s katerimi bomo lahko neposredo naslovili okvarjene gene in s tem genetske kardiomiopatije zdravili tudi vzročno.

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SLIKOVNE METODE V ELEKTROFIZIOLOGIJI

IMAGING MODALITIES IN ELECTROPHYSIOLOGICAL PROCEDURES

MRI AND CT IMAGING INTEGRATION WITH 3-D ELECTROANATOMICAL MAPPING SYSTEM FOR PLANNING OF THE CATHETER ABLATION PROCEDURE

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Introduction

Traditionally electrophysiologists tackling with ventricular arrhythmias have combined the intracardiac ECG with invasive catheter electroanatomical mapping to obtain a more detailed picture of the location of arrhythmia substrate.

Combining both methods with preprocedural cardiac imaging provides complementary information that increases precision and accuracy of substrate localization. Cardiac MRI has emerged as imaging modality of choice in identifying fibrotic areas in the ventricles and regional thinning of the ventricular myocardium. Identification of conducting channels is possible on the basis of LGE-CMR studies of the heart using three-dimensional (3D) scar reconstruction.

In addition, cardiac CT acurately depicts anatomy of the heart and great vessels as well as regional thinning of the ventricular myocardium.

Correlation between myocardial fibrosis parameters derived from late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) and arrhythmogenic substrate for VT has been well established in recent years.[1,2] LGE-CMR seems to have a higher sensitivity for accurate arrhythmogenic substrate identification compared to CT imaging derived 3D reconstructions.[3]

Conducting channels (CCs) inside nonhomogenous fibrosis are considered an arrhythmia substrate and a probable slowly conducting isthmus of ventricular tachycardia (VT). Complete conducting channel elimination is essential in providing procedural non-inducibility of ventricular arrythmias during catheter ablation procedures. Additionally, it improves long term arrhythmia free survival.[4,5]

Contents

In our center, we have some experience with Automatic Detection of Arrhythmic Substrate (ADAS-3D, Galgo Medical ltd, Barcelona) that allows preprocedural cardiac MRI or CT based 3D reconstruction of ventricular scar as well as ventricular CC determination.

The integration of these reconstructions into the 3D electroanatomical mapping (EAM) system gives valuable information about the areas of thinned myocardium and location and size of the CC prior to actual real time electroanatomical mapping.

The described integration has the potential to impact parameters and outcome of catheter ablation procedures for treatment of VT in structural heart disease. Firstly, it can improve the accuracy and reduce the duration of mapping.

Secondly, by providing a colour-coded 3D image of all fibrotic abnormalities within the heart, this

postimaging modality has the potential to make workflows more efficient. Thirdly, it has the potential to reduce the extent of ablation, especially outside the low-voltage fibrotic areas. Finally, all this improvements can translate into procedures with better safety profiles.

We will demonstrate our preliminary results in selected patients integrating ADAS 3D derived models with CARTO 3D EAM system.

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ROLE OF MRI IMAGING IN THE CONTEXT OF SUDDEN CARDIAC DEATH RISK STRATIFICATION IN CARDIOMYOPATHIES

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Introduction

Sudden cardiac death (SCD) is one of the major causes of cardiovascular death. SCD results from ventricular arrhythmias (VA), commonly detected in non-ischaemic cardiomyopathies (NICM). ICD implantation is associated with reduced all-cause mortality and is recommended in patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF). However, many recent studies and randomised control trials showed a limited value of SCD primary prevention strategies using risk stratification models based on LVEF only, especially in the NICM population.

The role of CMR

Cardiovascular magnetic resonance (CMR) currently provides the most accurate and reproducible measurement of atrial and biventricular systolic function and can detect changes in myocardial tissue structure. CMR is more sensitive than echocardiography to diagnose specific NICMs such as ARVC, LVNC, and apical HCM and has the potential to improve SCD risk stratification further. The latest "2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death" recommend using CMR for fibrosis detection by LGE in various NICMs in the context of ICD implantation (1). CMR parameters, such as late gadolinium enhancement (LGE), T1 relaxation times, and myocardial strain, have shown incremental value over LVEF in the prediction of SCD.

Late gadolinium enhancement

Gadolinium is an exclusively extracellular contrast agent washed out immediately from normal myocardium. However, in the presence of regional myocardial injury, e.g., necrosis, oedema, interstitial or replacement fibrosis, gadolinium would bind to excessive extracellular tissue and make it look brighter. The prognostic value of the presence, extent, location, and pattern of LGE for adverse outcomes, including SCD, has been demonstrated in multiple studies (2).

In dilated cardiomyopathy (DCM), several studies showed that myocardial scar by LGE is a predictor of adverse outcomes, independently from traditional risk factors such as EF. Studies focusing on a specific subset of DCM, such as patients with lamin A/C mutations or muscular dystrophies, could also confirm the prognostic relevance of LGE in assessing VA and SCD. Furthermore, the extent and location of the scar are important. Having a scar of more than 5% of LV mass and an EF > 30% would put you at higher risk for VA than having an LVEF < 30% and no or minimal scar. Some studies reported that linear septal mid-wall, patchy subepicardial and multiple locations LGE patterns in DCM are associated with a higher risk for VA.

In hypertrophic cardiomyopathy (HCM), LGE is present in almost 50% of patients, most commonly within the hypertrophied segments of the myocardium and at LV/RV insertion points. It was shown that an LGE extent ≥ 15% of LV mass was associated with a two-fold increase in risk for SCD.

Restrictive cardiomyopathy (RCM) is a heterogeneous group of diseases often in the context of systemic, inflammatory, storage or infiltrative disorders. LGE patterns provide an important insight into the pathophysiological process and have a prognostic value in this population. However, few studies address SCD as a specific endpoint since the death in this population is mainly related to non-cardiac causes.

T1 mapping and extracellular volume

Novel CMR techniques such as T1 mapping and assessment of extracellular volume (ECV) can predict SCD and arrhythmic events. In contrast to LGE, T1 mapping and ECV imaging can detect and quantify diffuse myocardial fibrosis. T1 mapping measures absolute values of T1 relaxation times of the myocardium pixel-wise, thus reflecting myocardial tissue composition. Myocardial ECV, on the other hand, refers to the space or volume of a tissue which is not occupied by cells and can be estimated from myocardial and blood T1 times before and after contrast agent administration as well as the haematocrit.

In DCM, native T1 values and ECV provide high diagnostic accuracy, sensitivity, and specificity in discriminating normal and diffusely diseased myocardium even when LVEF is only mildly reduced. In patients with ICD, studies showed that native T1 mapping was independently associated with appropriate ICD firing or documented sustained VT. Remarkably, the association persisted even after correction for the LGE burden.

In HCM, increased values in T1 maps and ECV were described in genotype-positive phenotype negative patients and can be used as an early imaging biomarker of the disease. Moreover, some studies have demonstrated that ECV has more robust predictive effectiveness than LGE since it showed independent predictive significance for SCD and VA even in the subgroup with LGE (3).

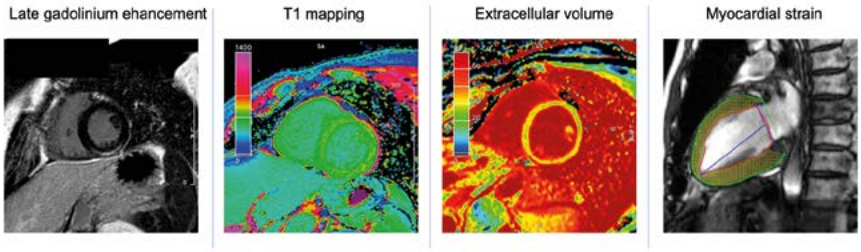
Myocardial strain

CMR feature tracking (CMR-FT) is currently the most feasible method for myocardial strain assessment, as tracking can be applied to standard cine images, and no additional sequences are needed. It has been known that myocardial strain is altered by fibrosis; therefore, it could be valuable for predicting VA. Even though CMR studies focused solely on arrhythmic endpoints in NICM are few, there is data from echocardiography strain studies and a good correlation between global longitudinal strain (GLS) obtained by CMR-FT and echocardiography was shown. In DCM, CMR-FT found impaired GLS to be independent prognostic parameters for a composite cardiac endpoint of cardiac death, heart transplantation, and aborted SCD. Strain values were superior in risk prediction compared to NYHA, EF, and LGE. In HCM, GLS was associated with all-cause mortality, hospital admission related to HF, lethal VA, or cardiovascular death (4). A review of 14 myocardial strain studies identified an association between impaired LV GLS and cardiovascular mortality and ICD firing.

Take-home message

SCD primary prevention strategies using risk stratification models based on LVEF only are of limited value in NICMs. Echocardiography is the first-line modality, but CMR has superior diagnostic and prognostic accuracy. CMR techniques, including the presence, extent, and distribution of LGE, T1 mapping, ECV, and strain, have incremental value to SCD risk stratification. Finally, no single risk factor to date has the discriminant power for safely identifying patients at risk for SCD. Thus, clinical, genetic, ECG and imaging parameters should be considered simultaneously.

Figure 1: CMR imaging biomarkers associated with sudden cardiac death.



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UPORABA NOVEGA DIELEKTRIČNEGA TRIDIMENZIONALNEGA SISTEMA V ELEKTROFIZIOLOGIJI – PRIKAZ PRIMEROV

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Uvod

Navigacija katetrov v virtualnem tridimenzionalnem (3D) prostoru je postala stalnica pri minimalno invazivnih elektrofizioloških posegih. Ob tem je zadnja leta velik poudarek na uporabi tehnologij, ki zmanjšujejo potrebo po uporabi škodljivih rentgenskih žarkov. Ti namreč predstavljajo breme tako za bolnika kot za izvajalce. Eden od takšnih sistemov je tudi Kodex – EPD. Slabosti trenutnih sistemov so visoka cena, nepremična oprema, vezana na določen laboratorij, uporaba točno določenih katetrov, možen 3D izris le ob točkovnem dotikanju tkiva ter dolga učna krivulja. V tokratnem predavanju bomo predstavili uporabo sistema Kodex v praksi in ugotovljene prednosti in slabosti.

Primeri

S pomočjo omenjene platforme smo opravili 3 primere. Začetna priprava bolnikov je preprosta. Namesti se šest nalepk, ki ustvarijo električno polje in sicer v treh ravninah. Bolnik med posegom leži, a se lahko tudi premakne, saj so nalepke fiksirane na telo. Kot je bilo že opisano, katetre sistem prikaže s pomočjo sprememb potencialov (v milivoltih), ki jih povzroča gibanje katetra v prostoru. Prav tako s pomočjo razlike v potencialih in napetostih med elektrodami ob znani razdalji med elektrodami ustvari notranje ravnilo, ki ga nato uporablja pri nadaljnjih izračunih. Kar se tiče izrisa 3D mape, sistem izkorišča dielektrične lastnosti bioloških tkiv. S pomočjo premikanja katetra v polju sistem izračunava razlike v napetostih, ki se še posebej pomembno spremenijo tik ob steni tkiva. Tako lahko sistem napove mejo votline in izriše steno votline brez potrebnega stika katetra s tkivom.

Izrisovanje je dokaj intuitivno. Že med uvajanjem katetrov se sproti riše venska karta, kar olajša pozicioniranje, prav tako pa pomembno zmanjša sevanje med posegom. Ob nastavitvi diagnostičnih katetrov (npr. dekapolarni) v desni atrij se takoj prične izrisovati oblika votline, dokaj natančno se prikaže Kochov trikotnik, ustje koronarnega sinusa ter ostala anatomija. Podobno je tudi z izrisom desne prekatne votline in iztočnega trakta.

Opravili smo poseg pri bolniku z atrijsko undulacijo, bolniku z AV nodalno tahikardijo in bolniku s prekatnimi ekstrasistolami. Podobno kot pri drugih sistemih tudi Kodex omogoča označevanje ablacijskih točk ter prikaz pritiska na tkivo, ki pa ni tako natančen kot je pri sistemu Carto. Prednost sistema je pogled od znotraj, ki je bolj natančen, kot to omogočajo druge platforme. Prav tako se mapa izredno hitro in tudi ves čas posodablja. Pomembna je tudi dobra podpora inženirskega tima, od katere je odvisno, kako hitro se prilagaja delu v laboratoriju. Kar se tiče uporabe RTG sevanja, je bilo to pomembno manjše kot je običajno pri teh posegih.

Žal sistem zaenkrat ni omogočal prikaza globine lezije ali debeline tkiva. Prav tako je trenutno nekaj logističnih težav pri zagotavljanju izvedbe nadaljnjih posegov in podpore s strani proizvajalca.

Ključno sporočilo

Kodex sistem je nova platforma, ki omogoča hitro in intuitivno izrisovanje tridimenzionalne strukture srca, dovoljuje uporabo širokega nabora katetrov in omogoča predvsem boljšo anatomsko orientacijo pri preprostejših posegih, kot so ablacije v desnih srčnih votlinah, kjer načeloma uporaba 3D sistemov ni nujna. Prav tako omogoča boljše učenje in pomembno zmanjšuje uporabo RTG sevanja. Slabosti so zaenkrat predvsem v slabši logistični podpori s strani proizvajalca, kar bo potrebno popraviti. Prav tako bo resnična dodana vrednost sistema prikaz globine lezije in debeline abliranega tkiva.

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NEFARMAKOLOŠKE METODE PREPREČEVAJNA TROMBEMBOLIČNIH ZAPLETOV ATRIJSKE FIBRILACIJE

NONPHARMACOLOGICAL METHODS FOR PREVENTION OF THROMBOEMBOLIC COMPLICATION OF AF

KRITIČNI POGLED NA NEFARMAKOLOŠKE NAČINE PREPREČEVANJA TROMBOEMBOLIČNIH ZAPLETOV ATRIJSKE FIBRILACIJE - POGLED NEVROLOGA

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Uvod

Atrijska fibrilacija (AF) je najpogostejša motnja srčnega ritma, ki vodi v razvoj kardioembolične ishemične možganske kapi (IMK). Metaanalize in velike randomizirane kontrolirane raziskave so nedvomno dokazale, da imajo ne-vitamin K oralna antikoagulacijska (NOAK) zdravila primerljivo učinkovitost v preprečevanju ishemičnih dogodkov kot antagonisti vitamina K, ob tem pa povzročijo manj velikih krvavitev, zato so NOAK zdravila prvega izbora v sekundarni preventivi IMK. Hemoragična kap na peroralnem antikoagulacijskem zdravljenju je redek dogodek, hkrati pa so ti bolniki velik izziv v nadaljnjem zdravljenju po utrpeli hemoragični kapi. Pri bolnikih, pri katerih z nevrološkega stališča opredelimo, da imajo absolutno kontraindikacijo za uvedbo antikoagulacijske terapije, je perkutana vstavitev zapirala v levo avrikulo možen in uspešen način zdravljenja.

Vsebina

Atrijska fibrilacija je najpogostejša motnja srčnega ritma, ki vodi v razvoj IMK. NOAK so zdravila prvega izbora pri bolnikih s kardioembolično IMK. Kljub visoki učinkovitosti in varnosti NOAK, nizek odstotek bolnikov utrpi ponovno IMK ali hemoragično možgansko kap. Razvoj hemoragične kapi in tudi IMK je pogostejši pri bolnikih, ki so zdravljeni z varfarinom.

Bolniki, ki na oralnem antikoagulacijskem zdravljenju utrpijo hemoragično kap predstavljajo velik izziv v nadaljnjem zdravljenju. Podatki o prognozi in pogojih za morebitno ponovno uvajanje NOAK pri bolnikih, ki so utrpeli znotrajlobanjsko krvavitev (ZLK) ob zdravljenju z NOAK, so pomanjkljivi. Ti bolniki so po eni strani brez ponovne zaščite zelo ogroženi za pojav IMK, po drugi pa jih ob uvedbi NOAK ogroža pojav ponovne ZLK. Smernice EHRA so precej ohlapne glede ponovnega uvajanja AKZ po ZLK na NOAK, pri čemer poudarjajo predvsem pomen izključitve vzroka krvavitve. V zadnjih letih se obsežno raziskuje cerebralna amiloidna angiopatija (CAA), ki je povezana z visoko pojavnostjo razvoja spontanih znotrajmožganskih krvavitev (ZMK). CAA je bolezen, pri kateri se v žilni steni odlaga patološki protein amiloid, kar vodi v razvoj krvavitev. Diagnoza CAA se postavi na osnovi Bostonskih ali Edinburških kriterijev. Smernice EHRA na podlagi mnenja ekspertov odsvetujejo uvedbo NOAK pri bolnikih s CAA, ki imajo več kot 10 mikrokrvavitev na susceptibilno poudarjenem slikanju (SWI) obtežene sekvence magnetnoresonančne tomografije (MRT) glave.

Pri bolnikih, pri katerih je uvedba antikoagulacijske terapije absolutno kontraindicirana, je možnost zdravljenja teh bolnikov z vstavitvijo zapirala v levo avrikulo. Pomemben je dober in kritičen izbor teh bolnikov, zato je nujna multidisciplinarna obravnava (kardiolog, nevrolog, specialist iz

področja antikoagulacijskega zdravljenja). Glede na etiologijo ZLK se multidisciplinarni tim odloči glede postproceduralnega zdravljenja teh bolnikov. Najzahtevnejši bolniki so zanesljivo bolniki s CAA, saj je pri njih verjetnost tveganja za razvoj ZLK največja.

Jasnih smernic postproceduralnega zdravljenja po vstavitvi zapirala v levo avrikulo žal ni, so zgolj priporočila, ki pa so precej ohlapna, saj je teh bolnikov s to možgansko patologijo relativno malo. Priporočila pa temeljijo na konsenzu strokovnjakov iz tega področja.

V UKC Ljubljana imamo konzilije, ki delujejo na osnovi multidisciplinarne obravnave (kardiolog, nevrolog, specialist antikoagulacijskega zdravljenja), kar nam omogoča ustrezen izbor bolnikov, ki so kandidati za vstavitev zapirala v levo avrikulo. Rezultati zdravljenja naših bolnikov so dobri.

Ključno sporočilo

Bolniki z nevalvularno AF, ki imajo absolutno kontraindikacijo z nevrološkega stališča, so kandidati za vstavitev zapirala v levo avrikulo. Pomembna je multidisiplinarna obravnava teh bolnikov, ki vključuje tim kardiologa, nevrologa in specialista antikoagulacijskega zdravljenja. Poseben izziv v zdravljenju predstavljajo bolniki z ZLK, ki imajo CAA in tudi zanje se zdi možnost vstavitve zapirala v levo avrikulo dober način zdravljenja.

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NEFARMAKOLOŠKE METODE PREPREČEVANJA TROMBEMBOLIČNIH ZAPLETOV PRI BOLNIKIH Z ATRIJSKO FIBRILACIJO – POGLED STROKOVNJAKA ZA ANTIKOAGULANTNO ZDRAVLJENJE

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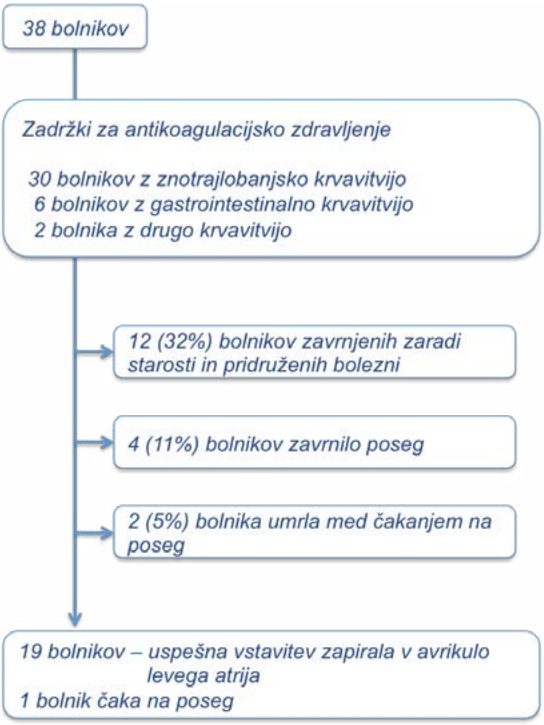
Uvod

Antikoagulacijsko (AK) zdravljenje je temeljni in najpomembnejši način za preprečevanje trombemboličnih zapletov pri bolnikih z atrijsko fibrilacijo. Čeprav izjemno učinkovito, AK zdravljenje prinaša povečano tveganje za krvavitve, od katerih so najbolj zaskrbljujoče velike krvavitve, ki zahtevajo hospitalizacijo, kirurški poseg in so lahko usodne za bolnika. Veliko krvavitev, ki neposredno ogrozi življenje, utrpi 2 – 5 % bolnikov, ki prejemajo peroralna AK zdravila. Znotrajmožganske krvavitve se pojavljajo pri 1 % bolnikov zdravljenih z varfarinom in pri 0,6 % bolnikov zdravljenih z neposrednimi peroralnimi antikoagulacijskimi zdravili (NOAK). Velike gastrointestinalne krvavitve so ob zdravljenju z NOAK vsaj enkrat pogostejše kot ob zdravljenju z varfarinom, utrpi pa jih okoli 2 % bolnikov. Vsi bolniki niso enako ogroženi za krvavitev ob AK zdravljenju. Najpomembnejša dejavnika tveganja za krvavitev sta starost in anamneza predhodnih krvavitev. Z naraščanjem uporabe NOAK predvsem pri starostnikih, je pričakovati, da bo število takšnih zapletov v porastu.

Ko po veliki krvavitvi prekinemo AK zdravljenje, je bolnik izpostavljen tveganju za trombembolični zaplet. Če se pojavi v obliki možganske kapi, prinaša veliko umrljivost, pri preživelih pa pogosto težke nevrološke posledice. Tako se znajdemo pred veliko dilemo ponovnega uvajanja AK zdravljenja bolnikom po veliki krvavitvi. Pri več kot polovici bolnikov se odločimo za trajno ukinitev zdravljenja. Bolniki, katerim ponovno uvedemo AK zdravljenje imajo kasneje manj trombemboličnih dogodkov, a tudi 2-krat večje tveganje za ponovno veliko krvavitev, kot bolniki pri katerih z AK zdravljenjem ne nadaljujemo. Najbolj so ogroženi bolniki, ki so utrpeli znotrajlobanjsko krvavitev in pri njih je dobrobit ponovnega uvajanja AK zdravljenja vprašljiva. Pri takšnih bolnikih je perkutano zapiranje avrikule levega preddvora lahko alternativa za tvegano nadaljevanje AK zdravljenja.

Bolniki-kandidati za zapiranje avrikule levega preddvora

Od leta 2017, ko je bil osnovan Konzilij za perkutano zapiranje avrikule levega preddvora, smo iz naše Antikoagulacijske ambulante predstavili 38 kandidatov (Slika 1). Bolniki so bili stari povprečno 72 (razpon 55 do 85) let, 19 je bilo moških, 19 pa žensk, po $CHADS_2$ točkovnu so dosegli povprečno 3 ± 1 točke. Kar polovica bolnikov je že utrpela možgansko kap. Vsi bolniki so, kot resen zadržek za nadaljevanje AK zdravljenja, imeli predhodno veliko krvavitev. Kar 30 bolnikov je utrpelo znotrajlobanjsko krvavitev, 26 ob AK zdravljenju, 4 pa brez njega. Šest bolnikov je utrpelo veliko gastrointestinalno krvavitev, 5 ob AK zdravljenju, eden brez njega. Preostala dva bolnika sta ob AK zdravljenju krvavela iz urotrakta oziroma v očesno steklovino.



Slika 1. Prikaz poti 38 bolnikov predstavljenih na Konziliju za zapiranje avrikule levega preddvora iz Antikoagulacijske abulante Kliničnega oddelka za žilne bolezni.

Skoraj 1/3 bolnikov je bilo za poseg zavrnjenih, večina zaradi starosti in krhkosti, nekaj pa zaradi pridruženih bolezni, ki bi lahko vplivale na uspešnost posega. Le pri 4 zavrnjenih bolnikih smo kljub veliki ogroženosti za ponovno krvavitev, nadaljevali z AK zdravljenjem, dvema smo predpisali aspirin, pet jih ne prejema nobenega protitrombotičnega zdravljenja, eden je umrl.

Štirje bolniki, primerni kandidati za poseg, posega niso želeli opraviti. En bolnik je umrl, trije so živi, med njimi le eden prejema AK zdravljenje.

Dve bolnici sta med čakanjem na poseg umrli, ena zaradi sepse, druga zaradi krvavitve.

Pri 19 bolnikih je bilo zapiranje avrikule levega preddvora uspešno opravljeno. Po posegu jih je 14 prejemalo dvojno antiagregacijsko zdravljenje, eden samo aspirin, 4 pa so potrebovali AK zdravljenje zaradi neoptimalne lege zapirala.

Ključno sporočilo

Vstavitev zapirala v avrikulo levega preddvora je pomembna nefarmakološka alternativa AK zdravljenju, predvsem pri bolnikih, ki so ob AK zdravljenju že utrpeli veliko krvavitev. Seveda obstajajo še neodgovorjena vprašanja kot so starostna meja oziroma pričakovana življenjska doba kandidata za poseg, optimalno antiagregacijsko zdravljenje po posegu, alternativni posegi pri bolniku z znanim strdkom v levi avrikuli in kontraindikacijo za AK zdravljenje, itd. Na nekatera nam bodo dale odgovore raziskave, ki so v teku, na druga bomo skušali odgovoriti sami, z multidisciplinarnim pristopom.

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NOVE MOŽNOSTI ELEKTROSTIMULACIJE SRCA

EMERGING STRATEGIES IN CARDIAC STIMULATION

CARDIAC STIMULATION IN ATRIOVENTRICULAR DROMOTROPATHY

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Introduction

Atrioventricular (AV) dromotropathy stands for AV conduction delay marked by prolonged PR interval on the electrocardiogram (ECG), which translates to mechanical AV uncoupling with unfavourable hemodynamic consequences. A prolonged PR interval is associated with worse outcomes. There is limited data on whether cardiac stimulation with AV coupling improves outcomes in patients with AV dromotropathy.

Contents

An excessively prolonged PR interval causes premature atrial contraction during the early diastolic phase, leading to shorter diastolic ventricular filling. Following the atrial systole, there is a time interval before the ventricular systole ensues, during which blood flows back to the atrium (diastolic mitral regurgitation). Such an AV uncoupling results in lower ventricular filling and lower stroke volume. Due to these changes, patients may develop symptoms like palpitations and dyspnoea on exertion.

According to the 2021 ESC Guidelines on cardiac pacing, symptomatic first-degree AV block represents an IIa indication for permanent pacemaker (PPM) implantation, with a level of evidence C. The recommendation is based on several case reports and expert opinion. Early studies with right ventricular (RV) pacing did not show haemodynamic benefit or quality of life improvement of AV re-coupling. Furthermore, a high percentage of RV pacing may cause PPM-induced cardiomyopathy. The emergence of conduction system pacing in recent years makes AV recoupling without induction of ventricular dyssynchrony possible. A small mechanistic within-patient comparison study showed that AV optimised His bundle pacing (HBP) improved acute haemodynamic response compared to the intrinsic rhythm with prolonged PR interval, while RV pacing reduced it.

To evaluate the benefit of AV coupling with HBP in patients with AV dromotropathy, we designed a single-centre randomised cross-over study. We included symptomatic patients with first and second degree, Mobitz 1, AV block, a PR interval above 250 ms, evidence of mechanical AV dyssynchrony on echocardiography and inappropriate PR interval shortening on exercise testing. Exclusion criteria were reduced left ventricular ejection fraction, atrial fibrillation, sinus node disease, or wide QRS complex. Patients were implanted with a dual chamber (DDD) PPM with a ventricular lead positioned on the His bundle. Patients were randomised into AV-optimised DDD pacing and backup pacing (VVI 40) arms. After three months, we performed a cardiopulmonary exercise test (CPET) and echocardiography. After that, the patients were crossed-over with follow-up after another three months. Primary outcome measures were changes in exercise capacity measured by peak oxygen consumption on CPET, left ventricular stroke volumes and quality of life using the 5-level EQ-5D questionnaire. Between January

2020 and September 2022, 17 patients were included. The completion of follow-up and results of the study are expected in January 2023.

A core Image

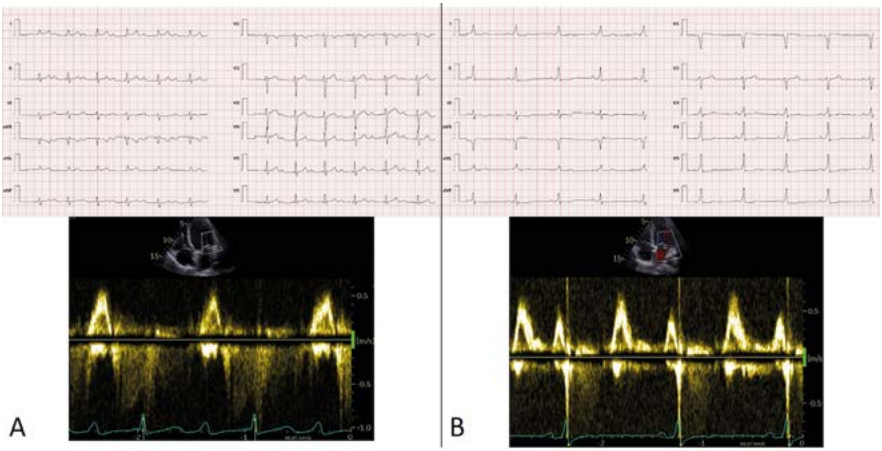

Figure 1: 12-lead ECG and transmitral pulsed wave (PW) doppler flow in a patient with AV dromotropathy before (A) and after (B) pacing therapy

Take-home Message

AV dromotropathy stands for prolonged PR interval with mechanic AV uncoupling, which causes symptoms due to reduced ventricular filling. Data shows that AV-optimised HBP improves acute haemodynamic response in these patients. Further studies are needed to establish whether this also translates into clinical benefit.

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TREATMENT OPTIONS IN PACING- OR TACHYCARDIA-INDUCED CARDIOMYOPATHY

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Introduction

Right ventricular (RV) pacing-induced electromechanical dyssynchrony and tachycardia-induced cardiomyopathy are well established risk factors of mortality and morbidity. The pursuit of alternate pacing sites including RV septum and RV outflow tract produced only modest or no clinical benefits (1). Furthermore, several device programming algorithms to minimize ventricular pacing were developed which are ineffective with advanced atrioventricular (AV) block and mainly function at the expense of AV dyssynchrony further increasing the risk of atrial fibrillation (AF) and heart failure (HF) (2). Compared to RV pacing, biventricular (BIV) pacing derived better results in patients with AV block and systolic dysfunction, however, the benefit was much less distinct in patients with preserved ejection fraction (3).

Conduction system pacing in pacing-induced cardiomyopathy

To avoid the detrimental effects of pacing dyssynchrony a new concept, conduction system pacing (CSP), including His bundle Pacing (HBP) and left bundle branch area pacing (LBBAP), was proposed as a potential alternative to prevent and reverse pacing-induced cardiomyopathy. Early work from Deshmukh et al. in 2000 showed feasibility of HBP. In 2017, Huang reported the first case of LBBP technique, which overcame some of the limitations of HBP. Nonetheless, both CSP modalities offer substantial advantages over RV or BIV pacing by allowing normal infrahisian conduction, consequently providing the physiological activation, avoiding cardiac dyssynchrony and left ventricular dysfunction (1). Although HBP is theoretically the *ideal* physiological pacing site, it has some inherent limitations. The implant technique is challenging and requires greater expertise in targeting a small zone. Long procedural and fluoroscopic times, high pacing capture thresholds, their rise during long-term follow-up and consequently early battery depletions could be observed. On the other hand, LBBP overcame most limitations associated with HBP, in turn, becoming more clinically feasible pacing option to adopt in clinical practice (4).

Conduction system pacing in tachycardia-induced cardiomyopathy

European Society of Cardiology (ESC) guidelines for the management of supraventricular tachycardia recommend atrio-ventricular node ablation (AVNA) with subsequent pacing ('pace and ablate') when tacycardia responsible for tachycardia-mediated cardiomyopathy cannot be ablated or pharmacologicaly controlled (Class I, level of evidence C). Recommeneded pacing modalities are either BIV or HBP. Several observational studies have already proved better clinical and echocardiographic

outcomes of HBP compared to BIV in symptomatic AF patients who underwent AVNA. Similarly, as in bradycardia indications, LBBAP seems a better option compared to HBP as it prevents the need of a back-up lead and facilitates subsequent AVNA (6).

Take-home message

Conduction system pacing modalities are feasible options to treat and prevent pacing- or tachycardia-induced cardiomyopathy. Compared to HBP, LBBAP offers more stable pacing parameters with similar clinical outcomes. However, LBBAP widespread clinical adaptation needs improvement of delivery tools and further validation in randomized clinical trials to ascertain its safety and efficacy.

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NOVOSTI NA PODROČJU KATETRSKE ABLACIJE ATRIJSKE FIBRILACIJE

UPDATE IN CATHETER ABLATION OF ATRIAL FIBRILLATION

LIGAMENT OF MARSHALL ALCOHOL ABLATION IN AF - WHEN AND HOW

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Introduction

Anatomical location of vein of Marshall (VOM) coincides with the location of the mitral isthmus and is commonly ablated to treat peri mitral flutter but on the other hand it contains autonomic innervation that triggers atrial fibrillation (AF) its location coincides with areas usually ablated during pulmonary vein antral isolation. Due to extensive sympathetic and parasympathetic innervation it serves as an important arrhythmogenic substrate and source of ectopic beats and usually successful area for ablation procedure. Alcohol ablation of VOM is presently considered a legitimate and a very successful therapeutic procedure.

Contents

In the present abstract I am presenting 5 very similar cases from our VOM population due of redo RF ablation patients treated for persistent atrial fibrillation (AF), with very stubborn relapses after successful ablation procedure and period of sinus rhythm, with relapses of macro reentrant atrial tachycardia and/or AF. All the patients went through several unsuccessful standard RF ablation procedures 2.6 ± 0.5 (bilateral antral PV isolation, linear ablation, and focal ablation at posterior LA site) and had relapses of macro-reentrant AT or persistent AF instead to additional AA therapy. In 3 of the patients alcohol ablations of VOM were performed at the end of redo RF ablation procedure and in 2 as a single isolated procedure. In all the cases sinus rhythm returned spontaneously (in 2 during second alcohol infusion and in 3 later in next 48 hours on the ward) no serious side effects were present only in 1 case a short term pericarditic pain with increase of CRP without pericardial effusion or ECG changes as an isolated pericarditis was present after 24 hours, successfully responded to anti-inflammatory medications. In the next part I am presenting my approach to VOM canulation, tips and tricks for successful and safe alcohol infusion as the attention on some important signs to omit potential serious side effects will be discussed.

Take-home message

To our knowledge VOM alcohol ablation is highly successful and if performed according to standard clinical practice relatively safe procedure.

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NOVOSTI NA PODROČJU KATETRSKE ABLACIJE PREKATNE TAHIKARDIJE

UPDATE IN CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

FLUOROLESS ABLATION OF VENTRICULAR TACHYCARDIA

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Introduction

Catheter ablation guided by conventional fluoroscopy is an established treatment option for ventricular arrythmias (VA). Reduction of radiation exposure during catheter ablation procedures with employing the ALARA (as low as reasonably achievable) principles is an already established routine in electrophysiology laboratories. However, with the complex nature of most procedures, radiation exposure is a matter of concern for both the patient and the staff performing the procedure. Prolonged fluoroscopy times and doses have been traditionally reported during VA ablation even in the most experienced hands. In recent years reports of near zero fluoroscopy (NZF) or completely zero fluoroscopy (ZF) aproach to VA ablation have emerged.

Contents

As in majority of other complex arrythimias 3D electroanatomical mapping (EAM) is used as a foundation for mapping and navigation. Intracardiac echocardiography (ICE) is however the sine qua non of NZF or ZF VA ablation. ICE is used for providing guidance for guide-wire, long sheath and trans-septal needle during trans-septal puncture. It also provides further information about cardiac anatomy relevant for accurate and effective endocardial mapping and ablation (eg. achieving cahteter stability at certain cardiac regions such as papillary muscles, moderator band, observing direction and position of the long sheath and catheter loops, etc.). In case of ablation in the region of sinuses of Valsalva it can replace coronary angiography for visualitaion of the coronary artery ostia. It also facilitates timely detection of possible complications such as sudden tissue whitening preceding "steam pops", pericardial effusion, potential thrombotic masses in the heart cavities or on sheaths and catheters inserted into the heart, sudden deterioration of systolic function of the ventricles. When using ICE integraded into the 3D EAM module, 2D ICE image frames can be used to construct 3D anatomy of the ventricle, pappilary muscles, valves, aortic root, etc. which facilitates catheter movement and navigation during the procedure. In recent years emergence of guiding sheats with real-time sheath visualation, integrated into 3D EAM, has provided the operator additional sheath information, to enhance positioning and navigation of the ablation catheter.

In a study Jan, et al. we have shown that NZF or ZF aproach to catheter ablation is feasible and safe. Procedural outcomes were similar in both structural heart disease or structuraly normal hearts and not inferior to conventional fluoroscopy based aproach. This is consistent with previously and recently published similar studies. The complication rate and long term success rate were also comparable to previously published complication rates. Recently Troisi, et al. have shown that ZF approach does not

affect overall procedure times. The last but not least ZF approach relieves the operators and other staff in the EP laboratory from wearing the lead apron which in long term could decrese the prevelance of orthopedic injuries among the staff involved in the procedure.

Take-home message

Although the available literature is still relatively scarce, it shows that ZF or NZF aproach is feasible and safe treatment aproach for treatment of VA.

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STEREOTAKTIČNA RADIOTERAPIJA ZA ZDRAVLJENJE REFRAKTARNIH PREKATNIH TAHIKARDIJ

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Uvod

Stereotaktična radioterapija (SBRT) je nova metoda zdravljenja, ki se vedno bolj uveljavlja pri zdravljenju refraktarnih ventrikularnih motenj ritma.

Vsebina

Trenutno izborno zdravljenje ventrikularnih motenj ritma, ki so neodzivne na zdravljenje z zdravili, je katetrska ablacija z radiofrekvenčno energijo. V zadnjih letih se je pojavila nova metoda zdravljenja teh motenj ritma, ki prihaja v poštev predvsem pri pacientih, kjer je radiofrekvenčna ablacija kontraindicirana, neuspešna oziroma ni možna. Pri SBRT ventrikularnih motenj srčnega ritma v eni frakciji dovedemo 25 Gy ionizirajočega sevanja na tarčno območje prekatne mišice, s čimer dosežemo antiaritmični učinek, ki se sicer vzpostavlja tudi več tednov. Prvi je metodo opisal Sharma s sodelavci na prašičjem modelu leta 2010, opis prvega primera zdravljenja refraktarnih ventrikularnih motenj ritma s SBRT pri človeku pa je objavil Loo s sodelavci leta 2015. Širša elektrofiziološka skupnost je za metodo izvedela konec leta 2017, ko je Cuculich s sodelavci objavil serijo 5 primerov v NEJM. Breme ventrikularnih aritmij so uspeli znižati za 99,9 % (izključujoč prvih 6 tednov po aplikaciji SBRT) primerjajoč obdobje 3 mesecev pred SBRT z obdobjem po SBRT.

Natančen antiaritmični mehanizem delovanja SBRT še ni povsem pojasnjen. Klasična katetrska ablacija z radiofrekvenčno energijo povzroči termično poškodbo miocitov, ki vodi v akutno koagulacijsko nekrozo in posledično blok prevoda.

Pri pacientih, ki so jih zdravili s SBRT, so sicer občasno po več mesecih ugotovili nastanek fibroze, kar bi lahko pojasnilo kronično antiaritmično učinkovitost te metode. Vsekakor pa ta mehanizem ne more pojasniti akutnega antiaritmičnega učinka, ki se lahko vzpostavi že v enem dnevu. Raziskave na živalih so kot možen akutni antiaritmični učinek SBRT navedle funkcionalne elektrofiziološke spremembe, ki privedejo do pospešitve prevoda po srčni mišici. Na celični ravni so dokazali večjo ekspresije kanalčkov za natrij in koneksinov Cx43. V raziskavi Zhanga s sod. so klinično pri 19 pacientih po SBRT ugotovili nesignifikantno zožanje širine QRS, od teh sta imela dva robustno zožanje QRS za 25ms.

Pri pripravi pacienta na SBRT je najbolj pomembna določitev substrata, ki povzroča motnje ritma in ki je posledično tarčna zdravljenja. Pri tem uporabimo 12-kanalni EKG, elektroanatomske mape, ki jih pridobimo med eventuelnim invazivnim elektrofiziološkim posegom, MR srca, scintigrafijo ipd. Tarčno področje v sodelovanju s specialisti onkologije z radioterapijo vrišemo na 4D CT sliko srca. Slikovno vodeno obsevanje opravimo na linearnem pospeševalniku s 25 Gy v eni frakciji. Antiaritmični učinek se v večji meri vzpostavi v prvem tednu, dokončen pa ponavadi v 6 tednih. Učinek se kaže kot manjše

breme ventrikularnih motenj ritma, manjši potrebi po aktivacijah ICD, manjpi uporabi antiaritmikov in izboljšani kakovosti življenja.

Od takojšnjih neželenih učinkov je pričakovati utrujenost, slabost in dispepsijo, od poznih neželenih učinkov (> 3 mesece po SBRT) pa pojav radiacijskega pneumonitisa, ki je večinoma asimptomatski, perikardnega izliva in poslabšanja srčnega popuščanja. Pojav neželenih učinkov je odvisen tudi od lokacije obsevanega tarčnega volumna.

Zaenkrat smo na KO za kardiologijo v sodelovanju z Onkološkim inštitutom uspešno opravili SBRT pri dveh pacientih z refraktarnimi ventrikularnimi motnjami ritma.

Ključno sporočilo

Stereotaktična radioterapija ritma je obetavna neinvazivna metoda zdravljenja refraktarnih ventrikularnih motenj ritma.

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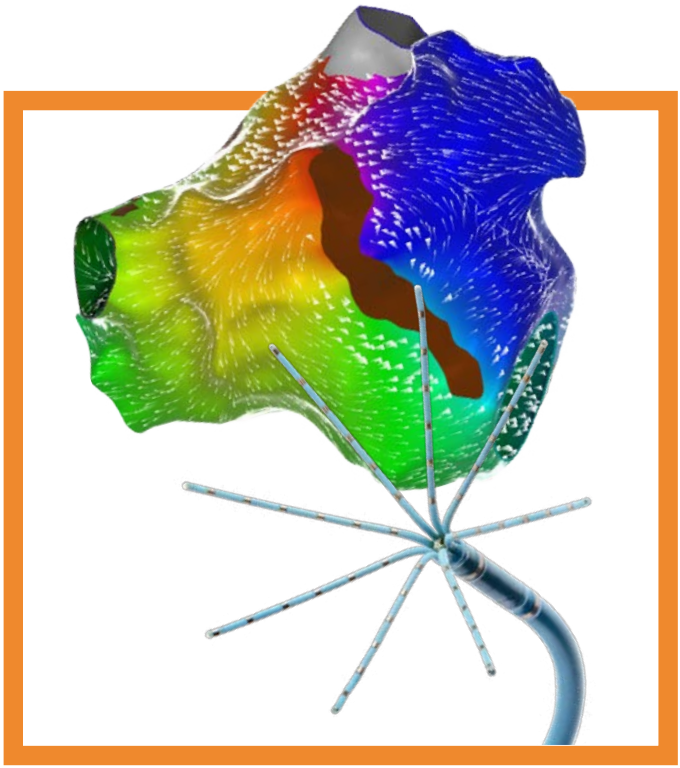

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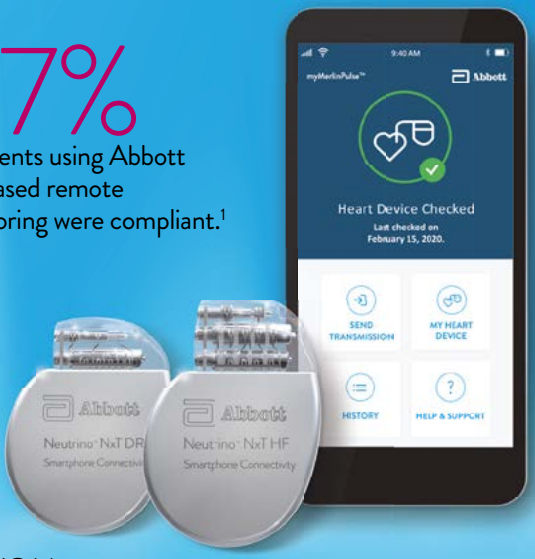

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Skrajšan povzetek glavnih značilnosti zdravila

Xarelto 10 mg / 15 mg / 20 mg filmsko obložene tablete
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Zdravljenje globoke venske tromboze (GVT) in pljučne embolije (PE) ter preprečevanje ponovne GVT in PE pri odraslih bolnikih. **15 mg/20 mg:** • Preprečevanje možganske kapi in sistemske embolije pri odraslih bolnikih z nevalvularno atrijsko fibrilacijo in enim ali več dejavniki tveganja, kot so kongestivno srčno popuščanje, hipertenzija, starost ≥ 75 let, sladkorna bolezen, predhodna možganska kap ali prehodni ishemični napad. • Zdravljenje globoke venske tromboze (GVT) in pljučne embolije (PE) ter preprečevanje ponovne GVT in PE pri odraslih bolnikih. • Zdravljenje venske trombembolije (VTE) in preprečevanje ponovne VTE pri otrocih in mladostnikih, mlajših od 18 let, in s telesno maso od 30 kg do 50 kg, po vsaj 5-dnevnem začetnem parenteralnem antikoagulacijskem zdravljenju. *Posebne skupine bolnikov:* • Samo za 15/20 mg: za odrasle bolnike z zmerno ali hudo okvaro ledvic veljajo posebna priporočila za odmerjanje. Posebna priporočila veljajo tudi za bolnike z GVT in PE, pri katerih je ocenjeno tveganje za krvavitve večje od tveganja za ponovno GVT in PE. Uporabe zdravila Xarelto se ne priporoča pri otrocih in mladostnikih z zmerno ali hudo okvaro ledvic. • Zdravilo Xarelto se lahko uvede ali z zdravljenjem nadaljuje pri bolnikih, pri katerih je potrebna kardioverzija. • Bolniki z nevalvularno atrijsko fibrilacijo, pri katerih je bila narejena perkutana koronarna intervencija (PCI - Percutaneous Coronary Intervention) z vstavitvijo žilne opornice: pri bolnikih z nevalvularno atrijsko fibrilacijo, ki potrebujejo peroralno antikoagulacijsko zdravljenje, in pri katerih je bila narejena perkutana koronarna intervencija z vstavitvijo žilne opornice, so izkušnje o uporabi zmanjšanega odmerka zdravila Xarelto 15 mg enkrat na dan (ali zdravila Xarelto 10 mg enkrat na dan pri bolnikih z zmerno okvaro ledvic [očistek kreatinina 30 - 49 ml/min]) skupaj z zaviralcem P2Y12 do 12 mesecev omejene. **ODMERJANJE IN NAČIN UPORABE:** *Preprečevanje venske trombembolije pri odraslih bolnikih po načrtovani kirurški zamenjavi kolka ali kolena:* Priporočeni odmerek je 10 mg rivaroksabana peroralno enkrat na dan. Prvi odmerek naj bi bolnik prejel 6 do 10 ur po kirurškem posegu, če je zagotovljena ustrezna hemostaza. Po velikem kirurškem posegu na kolku se priporoča 5-tedenska zaščita. Po velikem kirurškem posegu na kolenu se priporoča 2-tedenska zaščita. *Preprečevanje možganske kapi in sistemske embolije:* Priporočeni odmerek je 20 mg enkrat na dan, kar je tudi priporočeni največji odmerek. *Zdravljenje GVT in preprečevanje ponovne GVT in PE:* Priporočeni odmerek za začetno zdravljenje akutne GVT ali PE je prve tri tedne 15 mg dvakrat na dan, nato pa 20 mg enkrat na dan kot nadaljevanje zdravljenja in preprečevanje ponovne GVT in PE. *Bolniki z načrtovano kardioverzijo:* Pri bolnikih s kardioverzijo, vodeno s transezofagealnim ehokardiogramom (TEE), ki predhodno niso bili zdravljeni z antikoagulanti, je treba zdravljenje z zdravilom Xarelto začeti najmanj 4 ure pred kardioverzijo za zagotovitev ustrezne antikoagulacije. Pri vseh bolnikih je treba pred kardioverzijo pridobiti potrditev, da je bolnik jemal zdravilo Xarelto tako, kot je predpisano. *Zdravljenje VTE in preprečevanje ponovne VTE pri otrocih in mladostnikih:* Zdravljenje z zdravilom Xarelto pri otrocih in mladostnikih, mlajših od 18 let, je treba uvesti po najmanj 5-dnevnem začetnem parenteralnem antikoagulacijskem zdravljenju. Odmerek za otroke in mladostnike se izračuna glede na telesno maso. *Telesna masa 50 kg ali več:* priporoča se 20 mg rivaroksabana v enkratnem dnevnem odmerku. To je največji dnevni odmerek. *Telesna masa od 30 do 50 kg*: priporoča se 15 mg rivaroksabana v enkratnem dnevnem odmerku. To je največji dnevni odmerek. **KONTRAINDIKACIJE:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov; aktivna klinično pomembna krvavitev; poškodbe ali stanja z visokim tveganjem za velike krvavitve; sočasno zdravljenje s katerim koli drugim antikoagulantom razen v posebnih primerih zamenjave antikoagulacijskega zdravljenja ali kadar se nefrakcionirani heparini uporabljajo v odmerkih, ki so potrebni za vzdrževanje prehodnosti centralnega venskega ali arterijskega katetra; bolezen jeter, povezana z motnjami koagulacije in klinično pomembnim tveganje za krvavitve, vključno z jetrno cirozo razreda Child-Pugh B in C; nosečnost in dojenje. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Ves čas zdravljenja se priporoča klinično spremljanje v skladu s smernicami vodenja antikoagulacijskega zdravljenja. Zdravljenje z zdravilom Xarelto je treba prenehati, če se pojavijo hude krvavitve. S starostjo se tveganje za krvavitve lahko poveča. Zdravljenje z rivaroksabanom je treba prekiniti ob prvem pojavu hudega kožnega izpuščaja (tj. obsežen, intenziven in/ali mehurjast izpuščaj) ali katerega koli znaka probčutljivosti, ki se pojavi hkrati s spremembami na sluznicah. *Uporabe zdravila Xarelto se ne priporoča:* pri bolnikih s hudo okvaro ledvic (očistek kreatinina < 15 ml/min); pri otrocih in mladostnikih z zmerno ali hudo okvaro ledvic (glomerulna filtracija < 50 ml/min/1,73 m^2); pri bolnikih, ki sočasno jemljejo tudi močne zaviralce CYP3A4 in P-gp, t.j. azolne antimikotike za sistemsko zdravljenje ali zaviralce proteaz HIV; izogibati se je treba sočasni uporabi močnih induktorjev CYP3A4, razen če se bolnika skrbno spremlja glede znakov in simptomov tromboze; pri bolnikih, sočasno zdravljenih z dronedaronom; pri bolnikih z anamnezo tromboze in diagnozo antifosfolipidnega sindroma. Rivaroksaban se ne sme uporabljati za tromboprofilakso pri bolnikih, ki so pred kratkim prestali transkatetrsko zamenjavo aortne zaklopke (TAVR- transcatheter aortic valve replacement); pri bolnikih z umetnimi srčnimi zaklopkami ali pri bolnikih s pljučno embolijo, ki so hemodinamsko nestabilni ali ali morda potrebujejo trombolitično terapijo ali pljučno embolektomijo. *Previdna uporaba zdravila Xarelto:* Pri stanjih bolnikov, kjer obstaja povečano tveganje za krvavitve. Pri bolnikih s hudo okvaro ledvic (očistek kreatinina 15 – 29 ml/min); pri bolnikih z okvaro ledvic (15 in 20 mg) ali pri bolnikih z zmerno okvaro ledvic (očistek kreatinina 30 – 49 ml/min) (10 mg), ki sočasno uporabljajo druga zdravila, ki povečajo plazemsko koncentracijo rivaroksabana; pri bolnikih, ki sočasno prejemajo zdravila, ki vplivajo na hemostazo; pri nevraksialni anesteziji ali spinalni/epiduralni punkciji. Bolniki z aktivno rakovo boleznijo: treba je pretehtati korist zdravljenja z antitrombotiki in tveganje za krvavitve. Pri bolnikih, pri katerih obstaja tveganje za pojav razjed v prebavilih, je treba razmisliti tudi o ustreznem profilaktičnem zdravljenju. V vsakdanji praksi med zdravljenjem z rivaroksabanom ni potrebno spremljanje kazalcev koagulacije. Če je klinično indicirano, se lahko vrednosti rivaroksabana izmeri s kalibriranim kvantitativnim merjenjem aktivnosti anti-FXa. Zdravilo Xarelto vsebuje laktozo. **NEŽELENI UČINKI:** *Pogosti:* anemija, omotica, glavobol (pri otrocih zelo pogosto), krvavitev v očesu, hipotenzija, hematom, epistaksa (pri otrocih zelo pogosto), hemoptiza, krvavitev iz dlesni, krvavitve v prebavilih, bolečine v prebavilih in trebuhu, dispepsija, navzea, zaprtje, driska, bruhanje (pri otrocih zelo pogosto), povečane vrednosti transaminaz, srbenje, osip, ekhimoza, krvavitve v koži in podkožju, bolečine v okončinah, krvavitve v urogenitalnem traktu (menoragijo so opazili zelo pogosto pri ženskah < 55 let pri zdravljenju GVT, PE ali preprečevanju ponovne GVT ali PE; pogosto pri mladostnicah po menarhi), okvara ledvic, zvišana telesna temperatura (pri otrocih zelo pogosto), periferni edem, splošna oslabelost in pomanjkanje energije, krvavitev po posegu, kontuzija, sekrecija iz rane. *Občasni*: trombocitoza, trombocitopenija (pri otrocih pogosto), alergijska reakcija, alergijski dermatitis, angioedem in alergijski edem, cerebralna in intrakranialna krvavitev, sinkopa, tahikardija (pri otrocih pogosto), suha usta, okvara jeter, povečane vrednosti bilirubina (pri otrocih pogosto), povečane vrednosti alkalne fosfataze v krvi[A], povečane vrednosti GGT[A], urtikarija, hemartroza, slabo počutje, povečane vrednosti: LDH, lipaze, amilaze. *Redki*: zlatenica, povečane vrednosti konjugiranega bilirubina (pri otrocih občasno), holestaza, hepatitis (vključno s hepatocelularno poškodbo), krvavitve v mišicah, lokaliziran edem, vaskularna pseudoanevrizma. *Zelo redki*: anafilaktične reakcije vključno z anafilaktičnim šokom, Stevens-Johnsonov sindrom/toksična epidermalna nekroliza, sindrom DRESS. *Neznana pogostnost*: utesnitveni sindrom ali akutna odpoved ledvic po krvavitvi. **Način in režim predpisovanja ter izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet:** Bayer AG, 51368 Leverkusen, Germany **Datum zadnje revizije besedila**: 08/2021 **Za nadaljnje informacije o zdravilu Xarelto, se lahko obrnete na:** Bayer d.o.o., Bravničarjeva 13, 1000 Ljubljana / mi.slovenia@bayer.com **Verzija:** EU/14
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Slovenska aritmologija 2022

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