UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE

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T e z ă d e d o c t o r a t

TULBURĂRILE DE RITM ŞI DE CONDUCERE LA PACIENŢII CU SCLERODERMIE

– Rezumat –

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CUPRINS

Cuvinte cheie: sclerodermie, tulburări de ritm şi de conducere

PARTEA GENERALĂ

1. Introducere

Afectarea cardiacã în sclerodermie este corelatã cu un prognostic rezervat. Tulburările de ritm ventricular reprezintã principala cauzã de moarte cardiacã subitã la aceşti pacienți.

2. Manifestari cardiovasculare in sclerodermie

Afectarea cardiacã este frecventã la pacienții cu sclerodermie, cu o prevalență a manifestărilor clinice intre 15-35%. Afectarea cardiacã subclinicã este insã mult mai frecventã, aproximativ 60% din pacienti avand fibrozã miocardicã la examinarea RMN cardiac.

2.1 Fiziopatologie

Patogeneza exactã a fibrozei miocardice nu este pe deplin elucidatã. Se presupune ca mecanismul responsabil pentru depunerea de colagen la nivelul tegumentului este acelasi care determina fibroza miocardica, fiind reprezentat de vasospasmul arterelor mici.

2.2 Hipertensiunea pulmonarã

Prevalenta HTAP la pacientii cu sclerodermie este apreciata ca fiind intre 10-12%. Aceasta reprezinta una din principalele cauze de morbiditate si mortalitate la pacientii cu sclerodermie, fiind responsabila de pana la 30% din cauzele de deces.

2.3 Tulburarile de ritm si de conducere

Cele mai frecvente tulburari de ritm sunt: extrasistolele ventriculare izolate, cuplate, polimorfe, tahicardia ventriculara nesustinuta, urmate de extrasistolele atriale, flutterul atrial, fibrilatia atriala si tahicardiile paroxistice supraventriculare. Cele mai frecvente tulburari de conducere sunt : BRS, BAV I, BRD, tulburari de conducere intraventriculara nespecifice.

2.4 Pericardita

Tipurile de afectare pericardica intalnite includ pericardita acuta fibrinoasa, pericardita efuziva, aderente pericardice si pricardita cronica fibroasa. Prevalenta afectarii pericardice este intre 33% si 72%, in timp ce manifestarile clinice apar la 7% pana la 20% din subiecti.

2.5 Miocardita

Afecatrea miocardica este frecventa la pacientii cu sclerodermie. Caracteristica este reprezentata de fibroza miocardica. Distributia fibrozei miocardice e parcelara, la nivelul intregului miocard, afectand de regula ambii ventriculi. Cardiomiopatia atribuita procesului de fibroza miocardica apare la mai putin de 10% dintre pacienti.

2.6 Disfunctia ventriculara

Intre 11% si 29% din pacienti fara afectare cardiaca cunoscuta au FE% <50%, in timp ce la cei cu patologie cardiaca cunoscuta, procentul celor cu FE% <50% poate ajunge la 70-83%. Anomaliile de cinetica segmentara ale VS sunt frecvente, in timp ce anomalii ale functiei diastolice se intalnesc la 15% din pacienti. Anomalii ale functiei VD pot fi de asemenea prezente, pana la 35% din pacienti prezentand dilatarea VD si pana la 44% scadearea FE% a VD.

2.7 Afectarea circulatiei coronariene

Prevalenta aterosclerozei coronariene nu este crescuta la pacientii cu sclerodermie, fiind de aproximativ 22%, similar cu cel prezent in populatia generala. Pacientii cu sclerodermie pot prezenta angina pectorala chiar si atunci cand coronarografiile sunt normale.

2.8 Afectarea valvulara

Studiile ecocardiografice si necroptice efectuate la pacientii cu sclerodermie au demonstrat o afectare relativ putin frecventa (<1%) si in general minora a valvelor cardiace.

2.9 Disfunctia autonoma

Disfunctia autonoma este frecventa la pacientii cu sclerodermie, fiind in general subclinica. Cand este manifesta, ea include: fenomenul Raynaud, variatiile tensiunii arteriale, tahicardia sinusala, alterarea variabilitatii frecventei cardiace si a turbulentei frecventei cardiace.

3. Tulburarile de ritm si de conducere din sclerodermie

3.1 Date generale

Tulburarile de ritm si de conducere sunt frecvente la pacientii cu sclerodermie. Afectarea cardiaca structurala precum si incidenta crescuta a tulburarilor de ritm reprezinta un factor de risc pentru moartea subita cardiaca.

3.2 Epidemiologie

ECG-ul este modificat la 25-75% din pacientii cu sclerodermie sistemica.

3.3 Fizio-patologie

Mecanismele subjacente ale aritmiilor ventriculare in scleroza sistemica sunt complexe si posibil legate de fibroza miocardica difuza, scaderea perfuziei coronariene, vasospasmului dinamic, care promoveaza circuite de reintrare, automatism crescut si activitate trigger. Dintre aceastea, reintrarea este cel mai frecvent mecanism.

3.4 Tipuri de tulburari de ritm si de conducere

Cele mai frecvente tulburari de ritm sunt : ESV izolate, cuplate, polimorfe, TV nesustinuta. Extrasistolele atriale, flutterul atrial, fibrilatia atriala si tahicardiile aproxistice supraventirculare.

Cele mai frecvente tulburari de conducere din sclerodermie sunt : BRS, BAV I, BRD, tulburari de conducere intraventriculara nespecifice. BAV gr II si BAV gr III sunt rar intalnite.

3.5 Manifestarile clinice

Majoritatea pacientilor sunt asimptomatici. La pacientii simptomatici, cele mai frecvente simptome sunt reprezentate de: palpitatii, durere toracica, dispnee, pre-sincopa, sincopa, moarte cardiaca subita.

3.5 Diagnostic pozitiv

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3.6.1.2 Monitorizarea Holter ECG – prevalenta tulburarilor de ritm ajunge la 62%

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3.6.2.1 Studiul electrofiziologic – de regula precede terapia ablativa

3.6.2.2 Implantable loop recorder – recomandat cand Holter ECG este neconcludent

3.6.2.3 Interogarea dispozitivelor (pacemaker, ICD) utila la cei cu astfel de dispozitive

3.7 Prognostic

Afectarea cardiaca manifesta reprezinta un factor de prognostic negativ.. Aritmiile ventriculare se asociaza cu un risc crescut de mortalitate.

3.8 Complicatii

Prezenta aritmiilor ventriculare s-a corelat intr-un mod semnificativ cu mortalitatea de orice cauza si cu moartea subita.

3.9 Tratament

3.9.1 Medicatia antiaritmica

Medicatia antiaritmica joaca un rol important in tratamentul aritmiilor, dar nu exista in prezent studii clinice randomizate care au evaluat eficacitatea acestora in sclerodermie.

3.9.2 Tratamentul interventional

3.9.2.1 Stimulatorul cardiac - tratamentul de electie al tulburarilor severe de conducere.

3.9.2.2 Defibrilatorul cardiac implantabil – la cei cu aritmii ventriculare maligne

3.9.2.3 Ablatia cu radiofrecventa - adresata pacientilor refractari la medicatia antiaritmica. Experienta este insa limitata, un numar mic de astfel de cazuri fiind raportat in literatura.

PARTEA PRACTICĂ. CONTRIBUȚII PERSONALE

Scopul lucrării: caracterizarea tulburarilor de ritm si de conducere la pacientii cu sclerodermie, identificarea unor posibile corelatii intre prezenta tulburarilor de ritm si diverse caracteristici clinice si paraclinice ale bolii, determinarea profilelor cardiovasculare la pacientii cu tulburari de ritm si de conducere si identificarea pacientilor cu un risc cardiovascular crescut folosind metode de diagnostic neinvazive.

Studiul 1 – Prevalenta tulburarilor de ritm si de conducere determinata prin ECG si monitorizare Holter ECG la pacientii cu sclerodermie

Obiective

1. Identificarea si caracterizarea diverselor tipuri de tulburari de ritm si de conducere la pacientii cu sclerodermie folosind ECG de repaus 12 derivatii si monitorizare Holter ECG 24 de ore.
2. Determinarea profilelor cardiovasculare ale pacientilor cu sclerodermie si diversele tipuri de tulburari de ritm si de conducere.
3. Studiul relatiei dintre tulburarile de ritm si de conducere si anumite caracteristici clinice si paraclinice ale bolii: debutul fenomenelor Raynaud si non-Raynaud, prezenta comorbiditatilor, prezenta patologiei cardiovasculare asociate, parametri de laborator (nivelele serice de NT-pro BNP, auto-Ac: AAN, Ac anti Scl-70), medicatie cardiovasculara folosita, parametrii ecocardiografici.

Material şi metodă

Au fost luati in studiu 110 pacienti diagnosticati la Clinica de Reumatologie cu sclerodermie, atat forma sistemica cat si forma limitata, conform criteriilor American College of Rheumatology (ACR), femei si barbati, in perioada Noiembrie 2011 – Februarie 2015, cazuri consecutive.

Toti pacientii selectati si inclusi in studiu au fost adresati Clinicii de Cardiologie de la

Spitalul de Recuperare din Cluj-Napoca, unde li s-a efectuat: un examen clinic complet, ECG de repaus, evaluare ecocardiografica Doppler color, monitorizare Holter ECG 24 de ore. La un subgrup de 21 de pacienti atat cu cat si fara aritmii ventriculare s-au determinat nivelele serice ale NT-pro BNP**.**

Rezultate

1. Prevalenta totala a tulburarilor de ritm si de conducere a fost de 60.9%. A existat o suprapunere importanta a pacientilor cu aritmii si tulburari de conducere, 19% (n=21) prezentand atat aritmii supraventriculare cat si ventriculare, si 10% (n=11) avand ambele tipuri de tulburari de ritm plus o tulburare de conducere.

2. Pacientii cu tulburari de ritm si/sau de conducere au avut: varsta mai avansata ($p=0.05$), o prevalenta mai ridicata a hipertensiunii pulmonare ($p=0.008$), a valvulopatiilor moderate / severe ($p<0.001$), in special insuficienta mitrala si tricuspidiana, si a dilatarii camerale la examinarea ecocardiografica (atriala stanga si ventricualra dreapta, $p=0.012$, respectiv 0.005). Acesti pacienti au avut de asemenea nivele ale NT-pro BNP mai ridicate, 265.5 ± 399.5 pg/ml vs. 163 ± 140.1 pg/ml ($p=0.047$).

3. Exista o corelatie pozitiva intre severitatea tulburarilor de ritm ventricular si varsta, si una negativa cu FE% a pacientilor la echocardiografie.

Discuții

In studiul de fata a existat o prevalenta ridicata a tulburarilor de ritm si de conducere, de 60.9%, prevalenta comparabila cu cea raportata in alte studii.

Studii anterioare au demonstrat faptul ca aritmiile ventriculare sunt mai frecvente la pacientii cu anomalii ecocardiografice. In studiul de fata, pacientii cu aritmii si tulburari de conducere au avut mai frecvent anomalii echocardiografice comparativ cu pacientii fara tulburari de ritm si conducere. Relatia dintre nivelul mai ridicat al NT pro-BNP la pacientii cu aritmii ventriculare necesita studii ulterioare pentru confirmare.

Prezenta si anumite caracteristici ale tulburarilor de ritm s-au asociat cu diverse anomalii ecocardiografice.

Concluzii

Tulburarile de ritm si de conducere sunt frecvent intalnite la pacientii cu sclerodermie. Pacientii cu aritmii si tulburari de conducere sunt mai varstnici, au o prevalenta mai crescuta a hipertensiunii pulmonare, un grad mai ridicat de severitate al valvulopatiilor mitrale si tricuspidiene, o prevalenta mai ridicata a dilatarii atriale stangi si ventricualre drepte si niveluri serive ale NT-pro BNP mai ridicate comparativ cu pacientii cu sclerodermie fara aritmii si tulburari de conducere.

Studiul 2 – Evaluarea functiei autonome cardiace folosind analiza variabilitatii frecventei cardiace determinte cu ajutorul monitorizarii Holter ECG la pacientii cu sclerodermie

Obiective

1. Caracterizarea functiei autonome cardiace folosind analiza variabilitatii frecventei cardiace la un sublot de pacienti cu sclerodermie.
2. Stabilirea existentei unor eventuale asocieri intre prezenta disfunctiei autonome cardiace si prezenta tulburarilor de ritm si/sau de conducere.
3. Stabilirea existentei unor eventuale asocieri intre prezenta disfunctiei autonome cardiace si diversele caracteristici clinice si para-clinice ale pacientilor cu sclerodermie.

Material şi metodă

Din cei 134 de pacienti diagnosticati in Clinica de Reumatologie Cluj-Napoca cu sclerodermie, atat forma sistemica cat si forma limitata, conform criteriilor American College of Rheumatology, femei si barbati, in perioada Noiembrie 2011 – Iulie 2014, au fost inclusi in studiu 49 de pacienti.

Alti 49 de pacienti fara patologie cardio-vasculara cunoscuta, comparabili ca varsta si sex cu primul lot, internati pe sectia de Balneologie a Spitalului Clinic de Recuperare, femei si barbati, in perioada Aprilie 2012 – Iulie 2014 au constituit lotul de control.

Rezultate

La monitorizarea Holter ECG, pacientii cu sclerodermie au avut frecventa cardiaca minima si medie semnificativ mai ridicata comparativ cu lotul de control. In cadrul lotului de pacienti cu sclerodermie a existat o scadere semnificativa a valorilor urmatorilor parametri ai variabilitatii frecventei cardiace comparativ cu lotul de control: SDNN, SDANN, TI [-] si TINN.

In cadrul intregului lot de pacienti cu sclerodermie a existat o o corelatie negativa intre anumiti parametri ai VFC si numarul total de ExV decelate la monitorizarea Holter ECG.

A existat o corelatie pozitiva intre anumiti parametri ai VFC in domeniul temporal si durata fenomenul Raynaud si non-Raynaud si valoarea ecocardiografica a PAPs.

Discuţii

Pacientii cu sclerodermie au avut valori semnificativ mai crescute ale AV medii (atat diurne cat si noctrune) si minime la monitorizarea Holter ECG comparativ cu grupul de control, sugerand existenta unui tonus simpatic mai crescut. Acestia au prezentat valori mai scazute ale SDNN, SDANN, TI, TINN comparativ cu subiectii sanatosi, ceea ce denota existenta unui dezechilibrului simpatico-parasimpatic la nivel cardiac.

Pacientii cu disfunctie cardiaca autonoma asociaza alte anomalii clinice si paraclinice.

Identificarea disfunctiei autonome cardiace este importanta la pacientii cu sclerodermie si aritmii ventriculare. Acestia ar putea avea un prognostic mai rezervat, intrucat alterarea balantei sistemului simpato-parasimpatic este asociata cu cresterea riscului de aparitie a aritmiilor ventriculare maligne.

Concluzii

1. Pacientii cu sclerodermie prezinta disfunctie cardiaca autonoma subclinica.
2. Disfunctia autonoma cardiaca poate fi recunoscuta prin identificarea alterarii parametrilor ce caracterizeaza variabilitatea frecventei cardiace (SDNN, SDANN, TI si TINN).
3. Asocierea dintre prezenta si severitatea tulburarilor de ritm ventricular si disfunctia autonoma cardiaca necesita studii suplimentare.

Studiul 3 – Studiul relatiei dintre localizarea si pattern-ul fibrozei miocardice la examinarea RMN cardiac si prezenta tulburarilor de ritm ventricular

Obiective

1. Identificarea si caracterizarea fibrozei miocardice la pacientii cu sclerodermie folosind RMN cardiac.
2. Compararea rezultatelor examinarii RMN cardiac in functie de tipul de sclerodermie (difuza / limitata).
3. Evaluarea existentei unei eventuale corelatii intre prezenta fibrozei miocardice si tulburarile de ritm ventricular diagnosticate cu ajutorul monitorizarii Holter ECG.

Material şi metodă

Au fost luati in studiu un subgrup de 30 de pacienti, atat cu sclerodermie forma difuza cat si forma cutanata limitata, diagnosticati conform criteriilor American College of Rheumatology. Evaluarea pacientilor a inclus realizarea unui examen obiectiv complet, efectuarea de analize de laborator si o evaluare cardio-pulmonara (ECG 12 derivatii, monitorizare Holter ECG 24 ore, ecocardiografie Doppler transtoracica, spirometrie, radiografie pulmonara, si, atunci cand s-a considerat oportun, efectuarea de CT toracic de rezolutie inalta pentru identificarea fibrozei pulmonare). Ulterior, toti cei 30 de pacienti au efectuat RMN cardiac, cu administrare de gadolinium.

Rezultate

Prevalenta fibrozei miocardice a fost de 83.3% (87.5% la cei cu forma difuza vs. 78.5% la cei cu forma limitata, p=0.06). Fibroza a fost localizata cel mai frecvent intramural, afectand cu predilectie segmentele mijlocii si bazale ale ventriculului stang, cu un pattern predominant focal.

Pacientii cu sclerodermie difuza au avut FEVS% semnificativ mai scazuta la RMN cardiac.

Optsprezece pacienti (60%) au avut aritmii ventriculare sau tulburari de conducere pe ECG 12 derivatii sau monitorizare Holter ECG 24 de ore. In cadrul intregului grup de pacienti, numarul total de ExV inregistrat la monitorizarea Holter ECG s-a corelat cu numarul de segmente ale VS afectate de fibroza (r=0.36, p=0.04), cu prezenta fibrozei difuze (r=0.396, p=0.03).

Discuții

Prevalenta fibrozei miocardice identificata in studiul de fata este mai mare fata de cea raportata anterior (83.3% vs. 15-66%).

Pattern-ul si distributia fibrozei miocardice descrise la pacientii din studiul prezent au cateva trasaturi comune cu studiile publicate anterior pe aceasta tema: localizarea fibrozei a fost predominant intramiocardica la nivelul ventriculului stang, afectand mai ales segmentele din treimea mijlocie si bazala; distributia fibrozei nu a respectat un anumit teritoriu coronarian.

Exista o corelatie intre prezenta aritmiilor ventriculare si extensia fibrozei miocardice. Prezenta fibrozei miocardice difuze s-a corelat cu numarul total de extrasistole ventriculare.

Concluzii

1. Pacientii cu sclerodermie prezinta intr-o proportie semnificativa fibroza miocardica.
2. Aceasta este localizata cel mai frecvent intramural si nu respecta un teritoriu coronarian.
3. Extensia fibrozei miocardice influenteaza incarcatura aritmica.

Concluzii generale

1. Tulburarile de ritm si de conducere sunt frecvent intalnite la pacientii cu sclerodermie, avand o prevalenta de 60.9%.
2. Principalele tulburari de ritm intalnite in sclerodermie sunt: extrasistolele supraventriculare izolate, cuplete si in salve, precum si extrasistolele ventriculare izolate si cupletele.
3. Principalele tulburari de conducere intalnite la pacientii cu sclerodermie sunt: HBAS, BRD (minor si major), tulburarile de conducere intraventriculare nespecifice si BAV gradul I.
4. Pacientii cu aritmii si tulburari de conducere sunt mai varstnici, au o prevalenta mai crescuta a hipertensiunii pulmonare, un grad mai ridicat de severitate al valvulopatiilor mitrale si tricuspidiene, o prevalenta mai ridicata a dilatarii atriale stangi si ventricualre drepte si niveluri serive ale NT-pro BNP mai ridicate comparativ cu pacientii cu sclerodermie fara aritmii si tulburari de conducere.

5. Pacientii cu sclerodermie sistemica prezinta disfunctie autonoma cardiaca subclinica, manifestata printr-o alterare a parametrilor ce caracterizeaza variabilitatea frecventei cardiace
6. Disfunctia autonoma cardiaca fi diagnosticata cu ajutorul monitorizarii Holter ECG.
7. Pacientii cu sclerodermie prezinta intr-o proportie semnificativa fibroza miocardica.
8. Examinarea RMN cardiac “delayed enhancement” este o metoda de diagnostic neinvaziva ce poate identifica fibroza miocardica la pacientii cu sclerodermie.
9. Prezenta fibrozei miocardice difuze si numarul de segmente miocardice ale ventriculului stang afectate de fibroza par a influenta prezenta aritmiilor ventriculare si incarcatura aritmica.

„IULIU HAȚIEGANU” UNIVERSITY OF MEDICINE AND PHARMACY CLUJ-NAPOCA

P H D T H E S I S

ARRHYTHMIAS AND CONDUCTION DISORDERS IN PATIENTS WITH SCLERODERMA

– Summary –

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Keywords: scleroderma, arrhythmias and conduction disorders

GENERAL PART

1. Introduction

Cardiac involvement is correlated with a poor prognosis in patients with scleroderma. Ventricular arrhythmias represent the main cause of sudden cardiac death in this population.

2. Cardiovascular manifestations in scleroderma

Cardiac involvement is frequent in patients with scleroderma, with a prevalence of clinical manifestations of 15-35%. Subclinical cardiac involvement is even more frequent, approximately 60% of patients having myocardial fibrosis on cardiac magnetic resonance imaging (MRI).

2.1 Pathophysiology

The pathogenesis of myocardial fibrosis has not been fully elucidated. It is thought that the mechanism responsible for collagen deposition at the level of the skin is the same one which determines myocardial fibrosis, this being the vasospasm of the small arteries.

2.2 Pulmonary hypertensions

The prevalence of pulmonary hypertension is between 10-12% in patients with scleroderma. This condition represents one of the main causes of morbidity and mortality in patients with scleroderma, being responsible of up to 30% of the causes of death.

2.3 Arrhythmias and conduction disorders

The most common arrhythmias are: isolated and coupled polymorphic premature ventricular contractions, non-sustained ventricular tachycardia, atrial premature contractions, atrial flutter, atrial fibrillation and paroxysmal supraventricular tachycardias. The most common conduction disorders are: left bundle branch block, first degree AV block, right bundle branch block and non-specific intraventricular conduction disorders.

2.4 Pericarditis

The types of pericardial involvement include acute fibrinous pericarditis, effusive pericarditis, pericardial adhesions and chronic fibrinous pericarditis. The prevalence of pericardial involvement ranges between 33 and 72%, while clinical manifestations are found in 7% to 20% of subjects.

2.5 Myocarditis

Myocardial involvement is frequent in patients with scleroderma. Its landmark is myocardial fibrosis. The fibrosis is patchy and affects all layers of the myocardium, of both right and left ventricle. The cardiomyopathy attributed to myocardial fibrosis is found in less than 10% of the cases.

2.6 Ventricular dysfunctions

Between 11% and 29% of patients without known cardiac involvement have EF% of < 50%, while patients with known cardiac impairment, the percentage of patients with an EF < 50% can reach 70-83%. Regional kinetics abnormalities of the left ventricle are frequent, while diastolic dysfunction can be found in approximately 15% of patients. Right ventricular function abnormalities can also be found, up to 35% of patients having right ventricular dilation and un to 44% have a diminished EF% of the right ventricle.

2.7 Coronary circulation impairment

The prevalence of coronary artery atherosclerosis is not high in scleroderma patients, being of approximately 22%, similar to the one found in the general population. Patients with scleroderma can have angina pectoris even in the presence of normal coronary angiograms.

2.8 Valve impairment

Echocardiographic and necroptic studies performed in patients with scleroderma demonstrated a relatively low prevalence (<1%) of valve disease, with usually mild impairment.

2.9 Autonomic dysfunction

Autonomic dysfunction is frequent in patients with scleroderma and is usually subclinical. When manifest, it includes: Raynaud's phenomenon, blood pressure fluctuations, sinus tachycardia, heart rate variability and heart rate turbulence impairment.

3. Arrhythmias and conduction disorders in scleroderma

3.1 General findings

Arrhythmias and conduction disorders are frequent in patients with scleroderma. The presence of structural heart disease and the high incidence of rhythm disturbances represent risk factors for sudden cardiac death in this population of patients.

3.2 Epidemiology

An abnormal ECG is found in 25-75% of patients with scleroderma.

3.3 Pathophysiology

The underlying mechanisms of ventricular arrhythmias in systemic sclerosis are complex and possible related to the presence of diffuse myocardial fibrosis, the reduction in coronary perfusion and dynamic vasospasm, which promote reentry circuits, increased automaticity and trigger activity. Of these, reentry is the most frequent mechanism.

3.4 Types of arrhythmias and conduction disorders

The most frequent arrhythmias are: isolated and coupled polymorphic premature ventricular contractions and non-sustained ventricular tachycardia, atrial premature contractions, atrial flutter, atrial fibriallation and supravetricualr tachycardias. The most common conduction disorders are: left bundle branch block, first degree AV block, right bundle branch block and non-specific intraventricular conduction disorders. Second and third degree AV block are rare.

3.5 Clinical manifestations

Most of the patients are asymptomatic. In symptomatic patients, the most common symptoms are: palpitations, angina pectoris, dyspnea, pre-syncope, syncope and sudden cardiac death.

3.5 **Diagnostis**

3.6.1 Non-invasive diagnosis methods

3.6.1.1 12-lead ECG – performed on à cet rutine basis

3.6.1.2 Holter ECG monitoring – the prevalence of arrhythmias can reach 62%

3.6.1.3 Signal-averaged ECG – identifies a subgroup of patients who require further invetigations

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3.6.2.2 Implantable loop recorder –recommended when the Holter ECG is inconclusive

3.6.2.3 Device interrogation (pacemakers, ICDs) – useful in device carriers

3.7 Prognosis

Manifest cardiac impairment carries a poor prognosis. The presence of ventricular arrhythmias correlates with a high mortality risk.

3.8 Complications

The presence of ventricular arrhythmias correlates with all cause mortality and with sudden cardiac death.

3.9 **Treatment**

3.9.1 Antiarrhythmic medication

Antiarrhythmic drugs play an important role in the treatment of arrhythmias, even though there are no currently randomized control trials assessing their efficacy in patients with scleroderma.

3.9.2 Interventional treatment

3.9.2.1 Pacemaker – the gold standard treatment for conduction disorders.

3.9.2.2 Implantable cardioverter defibrillator – for malignant ventricular arrhythmias

3.9.2.3 Radiofrequency ablation – for patients refractory to antiarrhythmic drugs. The existing experience is however limited.

PRACTICAL PART. PERSONAL CONTRIBUTION

Aim: description of arrhythmias and conduction disorders in patients with scleroderma, identification of a possible correlation between the presence of arrhythmias and several clinical and paraclinical characteristics of the disease, description of cardiovascular profiles of scleroderma patients with arrhythmias and conduction disorders and identification of scleroderma patients with a high cardiovascular risk using invasive and non-invasive diagnostic methods.

Study 1 – Prevalence of arrhythmias and conduction disorders determined by 12-lead ECG and Holter ECG monitoring in patients with scleroderma

Objectives

1. Identification and description of arrhythmias and conduction disorders in patients with scleroderma using the 12-lead ECG and 24-hour Holter ECG monitoring
2. Description of cardiovascular profiles of scleroderma patients with arrhythmias and conduction disorders
3. Assessment of the correlation between arrhythmias and conduction disorders and several clinical and paraclinical characteristics of the disease (onset of Raynaud's and non-Raynaud's phenomenon, the presence of commorbidities, the presence of associated cardiovascular disease, laboratory markers (NT-pro BNP serum levels, auto-antibodies: ANA, anti-Scl-70), cardiovascular medication, echocardiographic parameters.

Material and methods

One hundred and ten patients with scleroderma, both the diffuse and the limited cutaneous

subtype, diagnosed according to the American College of Rheumatology (ACR) criteria at the Rheumatology Clinic in Cluj-Napoca, between November 2011 and February 2015, consecutive cases were included in the study.

All the patients were evaluated in the Cardiology Department of the Rehabilitation Hospital, Cluj-Napoca, by means of: a complete clinical examination, 12-lead ECG, transthoracic Doppler echocardiography and 24-hour Holter ECG monitoring. In a subgroup of 21 patients, regardless of the presence of ventricular arrhythmias, NT-pro BNP levels were measured.

Results

1. The prevalence of arrhythmias and conduction disorders was 60.9%. There was a significant overlap between patients with arrhythmias and patients with conduction disorders, 19% (n=21) having both supraventricular and ventricular arrhythmias, and 10% (n=11) having both arrhythmias and conduction disorders.

2. Patients with arrhythmias and conduction disorders had: a more advanced average age ($p=0.05$), a higher prevalence of pulmonary hypertension ($p=0.008$), of moderate/severe valve disease ($p<0.001$), especially mitral and tricuspid regurgitation, and of chamber dilation on echocardiography (left atrial and right ventricular, $p=0.012$ and $p=0.005$, respectively). These patients also had higher levels of NT-pro BNP, 265.5 ± 399.5 pg/ml vs. 163 ± 140.1 pg/ml ($p=0.047$).

3. There is a positive correlation between the severity of ventricular arrhythmias and the patients' age, and a negative one between the severity of ventricular arrhythmias and the EF%.

Discussion

In the present study there was a high prevalence of arrhythmias and conduction disorders, of 60.9%, which is comparable to previously reported data in the literature.

Previous studies have demonstrated that ventricular arrhythmias are more frequent in patients with echocardiographic abnormalities. In the present study, patients with arrhythmias and conduction disorders had more significant echocardiographic abnormalities compared to patients without arrhythmias and conduction disorders. The presence of higher NT-pro BNP levels in patients with ventricular arrhythmias needs further research.

We found correlations between the presence and several characteristics of arrhythmias and several echocardiographic parameters.

Conclusions

Arrhythmias and conduction disorders are common in patients with scleroderma. Patients with these condition are older, have a higher prevalence of pulmonary hypertension, more severe valve disease (mitral and tricuspid), a higher prevalence of left atrial and right ventricular dilation and higher NT-pro BNP levels compared to scleroderma patients without arrhythmias and conduction disorders.

Study 2 – Assessment of cardiac autonomic function using heart rate variability evaluation determined by Holter ECG in patients with scleroderma

Objectives

1. Characterization of autonomic function using heart rate variability (HRV) analysis in a subgroup of scleroderma patients
2. Characterization of autonomic function using heart rate variability analysis in scleroderma patients according to the scleroderma subtype (diffuse, limited).
3. Analysis of possible associations between the presence of autonomic dysfunction and the presence of arrhythmias and conduction disorders.
4. Analysis of possible associations between the presence of autonomic dysfunction and several clinical and paraclinical characteristics of scleroderma.

Material and methods

Among the 134 patients with scleroderma, both the diffuse and the limited cutaneous subtype, diagnosed according to the American College of Rheumatology (ACR) criteria at the Rheumatology Clinic in Cluj-Napoca, between November 2011 and February 2015, 49 consecutive cases were included in the study.

A group of 49 patients without cardiovascular diseases, age and sex-matched, from the Physical Rehabilitation Department of the Rehabilitation Hospital, admitted between April 2012 and June 2014 represented the control group.

Results

At Holter ECG monitoring, patients with scleroderma had a higher average and minimum heart rate compared to the control group. Among patients with scleroderma, the following heart rate variability parameters had significant lower values compared to the control group: SDNN, SDANN, TI [-] and TINN.

Among patients with scleroderma, there was a negative correlation between some HRV parameters and the total number of premature ventricular contractions on Holter ECG monitoring.

There was a positive correlation between some HRV parameters and the duration of Raynaud’s and non-Raynaud’s phenomenon and the echocardiographic value of sPAP.

Discussion

Patients with scleroderma had significant higher values of the average (both diurnal and nocturnal) and minimum heart rate on Holter ECG monitoring compared to controls, suggesting the presence of an increased sympathetic tone. Scleroderma patients also had lower values of SDNN, SDANN, TI, TINN compared to healthy subjects, a fact which supports the existance of a sympathetic / vagal imbalance on a cardiac level.

Patients with autonomic dysfunction associate other clinical and paraclinical abnormalities.

Identification of cardiac autonomic dysfunction in scleroderma patients with arrhythmias is important. These patients might have a worse prognosis, since the presence of a sympathetic / vagal imbalance is associated with the risk of malignant ventricular arrhythmias.

Conclusions

1. Patients with scleroderma have subclinical cardiac autonomic dysfunction.
2. Cardiac autonomic dysfunction can be detected by identifying alterations in parameters characterizing heart rate variability (SDNN, SDANN, TI and TINN).
3. The association between the presence and severity of ventricular arrhythmias and the presence of cardiac autonomic dysfunction requires further research.

Study 3 – Assessment of the correlation between the localization and the pattern of myocardial fibrosis revealed by cardiac MRI and the presence of ventricular arrhythmias

Objectives

1. Identification and characterization of myocardial fibrosis in patients with scleroderma using cardiac MRI.
2. Comparison of cardiac MRI findings according to the scleroderma subtype (diffuse vs. limited).
3. Assessment of a possible correlation between the presence of myocardial fibrosis and ventricular arrhythmias identified using 24-hour Holter ECG monitoring.

Material and methods

A subgroup of 30 patients with scleroderma, both the diffuse and the limited cutaneous subtype, diagnosed according to the American College of Rheumatology (ACR) criteria at the Rheumatology Clinic in Cluj-Napoca were included in the study.

The evaluation of patients included a complete physical examination, laboratory analysis, and a cardio-pulmonary evaluation (12-lead ECG, 24-hour Holter ECG monitoring, transthoracic Doppler echocardiography, spirometry, chest X-ray and, when considered necessary, high resolution chest CT for pulmonary fibrosis detection). Subsequently, all 30 patients underwent cardiac MRI, with gadolinium administration.

Results

The prevalence of myocardial fibrosis was 83.3% (87.5% in patients with diffuse scleroderma vs. 78.5% in patients with limited scleroderma, p=0.06). The localization of fibrosis

was most frequently intramyocardial, affecting mainly the middle and basal segments of the left ventricle, with a predominantly focal pattern.

Patients with diffuse scleroderma had significantly lower EF% on cardiac MRI.

Eighteen patients (60%) had ventricular arrhythmias or conduction disorders on the 12-lead ECG and Holter ECG monitoring. The total number of premature ventricular contractions on Holter ECG monitoring correlated with the number of fibrosis-involved segments of the left ventricle ($r=0.36$, $p=0.04$), with the presence of diffuse fibrosis ($r=0.396$, $p=0.03$).

Discussion

The prevalence of myocardial fibrosis from the present study is higher than the one reported in the literature (83.3% vs. 15-66%).

The pattern and distribution of myocardial fibrosis in patients from the present study have several common features with the one described in previously published studies: the mainly intra-myocardial localization of fibrosis at the level of the left ventricle, affecting mainly the middle and basal segments of the left ventricle; myocardial fibrosis is not found in a specific coronary artery territory.

There is a correlation between the presence of ventricular arrhythmias and the extent of myocardial fibrosis. The presence of diffuse myocardial fibrosis correlated with the total number of ventricular premature beats.

Conclusions

1. Patients with scleroderma have a high prevalence of myocardial fibrosis.
2. Myocardial fibrosis is mainly intra-myocardial and does not resemble fibrosis secondary to myocardial ischemia.
3. The extent of myocardial fibrosis influences the arrhythmic burden.

General conclusions

1. Arrhythmias and conduction disorders are frequent in scleroderma patients, with a prevalence of 60.9%.
2. The main arrhythmias encountered are: isolated, coupled and runs of premature atrial contractions, as well as isolated and coupled ventricular arrhythmias.
3. The main conduction disorders encountered are: left anterior fascicular block, right bundle branch block (minor and major), non-specific intraventricular conduction disorders and first degree AV block.
4. Patients with arrhythmias and conduction disorders are older, have a higher prevalence of pulmonary hypertension, a more severe degree of mitral and tricuspid valve disease, a higher prevalence of left atrial and right ventricular dilation and higher levels of NT-pro BNP compared to patients without arrhythmias and conduction disorders.
5. Patients with scleroderma have subclinical cardiac autonomic dysfunction, expressed by an alteration of parameters characterizing heart rate variability.
6. Cardiac autonomic dysfunction can be diagnosed using Holter ECG monitoring.

7. Patients with scleroderma have a high prevalence of myocardial fibrosis.
8. “Delayed enhancement MRI” is a non-invasive diagnostic method capable of identifying myocardial fibrosis in patients with scleroderma.
9. The presence of diffuse myocardial fibrosis and the extent of fibrosis influence the presence of ventricular arrhythmias and the arrhythmic burden.