REZUMATUL TEZEI DE DOCTORAT

DISRITMIILE ÎN CARDIOMIOPATIILE DILALATIVE DIAGNOSTIC, TRATAMENT ŞI PROFIL EVOLUTIV

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Diversele studii epidemiologie, care sunt probabile subestimative, raportează o incidență a cardiomiopatiei dilatative de aproximativ 20/100000/an şi o prevaență de 38/100000/an. Aceasta reprezintă a treia cauză etiologică a insuficienței cardiace şi prima cauza de transplant cardiac.

În ciuda îmbunătățirii tratamentului insuficienței cardiace, cardiomiopatia dilatativă continuă să reprezinte o imporatantă cauză de mortalitate cardiovasculară, în special prin tulburări de ritm. FiA este cea mai frecvent întâlnită aritmie în IC. Debutul său poate duce la agravarea simptomelor, un risc crescut al complicațiilor tromboembolice, şi un prognostic pe termen lung mai sever.

În acest context, lucrarea de fata a avut la baza premiza cresterii continue a incidentei insuficientei cardiace si secundar acesteia, cresterea cazurilor nou diagnosticate a cardiomiopatiilor dilatative. Descoperirea unei noi medicații eficiente in tratamentul insuficientei cardiace a crescut supravietuirea acestor bolnavi, dar in contrapartida a crescut incidenta tulburarilor de ritm prezentate de acestia. Prognosticul bolnavilor rămâne nefavorabil in special la cei care asociaza cardiomiopatie dilatativa cu insuficienta cardiaca congestivă.

În partea **teoretică** s-a realizat o evaluare a principalelor forme de cardiomiopatii, cu un accent special pe cardiomiopatia dilatativă, precum şi o trecere în revistă a mecanismelor implicate în patogeneza acesteia, dar şi a insuficienței cardiace. De asemenea s-au analizat toate formele de aritmii care pot reprezenta complicații ale cardiomiopatiei dilatative, atât din punct de vedere patogenetic, cât şi din punct de vedere a posibilelor atitudini terapeutice.

Partea specială a cuprins mai multe direcții de cercetare. În primul rând s-a realizat rând analiza profilului evolutiv al bolnavilor cu cardiomiopatie dilatativă şi tulburări de ritm aflați sub tratment cu amiodaronă şi incidența fibrilației atriale, de departe cea mai frecventă aritmie întâlnită în insuficiența cardiacă. Apoi există două capitole în care se analizează posibila relație dintre nivelul plasmatic al receptorului I solubil al factorului de necroză tumorală şi prezența fibrilației atriale, precum şi rolul inhibitorilor sistemului renina angiotensină-aldosteron în tratamentul fibrilției atriale din cardiomiopatia dilatativă complicată cu inuficiență cardiacă congestivă.

INCIDENȚA FIBRILATIEI ATRIALE LA BOLNAVII CU CARDIOMIOPATIE DILATATIVĂ

Scopul sudiului: evaluarea prevalenței fibrilației atriale (FiA) la bolnavii cu CMD internați în Clinica de Cardiologie Recuperare-Cluj Napoca.

Material şi metodă. Au fost luați în studiu un număr de 164 pacienți care au fost împărțiți în două loturi: lotul I- 136 bolnavi care au prezentat tulburări de ritm cardiac şi lotul II-28 pacienți cu CMD fără tulburări de ritm. S-au ananlizat tipurile de tulburări de ritm din lotul I, medicația antiartimică recomandată, precum şi caracteristicile comparative ale celor două loturi din punct de vedere al vârstei, sexului, factorilor de risc cardiovasculari, etiologiei ICC, parametrilor ECG şi ecocardiografici, monitorizării ECG Holter/24 de ore.

Rezultate. Prevalența tulburărilor de ritm la cei 470 pacienți cu ICC a fost de 82,9%.

În ceea ce priveşte etiologia CMD, în lotul I acesta a fost ischemică la 33.6 % (46) pacienți, toxică la 41.4 % (56), respectiv idiopatică la 25% (34) dintre aceştia. Etiologia CMD în lotul II a fost următoarea: ischemică la 28.2 % (8) pacienți, toxică la 14.8 % (4), respectiv idiopatică la 57% (16) dintre bolnavi. 76% din pacienți au beneficiat de monitorizare ECG Holter/24h.

Etiologia ischemică a fost identificată la 66,4% dintre pacienți cu tulburări de ritm existente în tratamentul diagnosticului CMD.

Realizând în lotul I o analiză a tulburării de ritm obiectivate prin ECG de repaus şi Holter-ECG/24 de ore am constatat următoarele:

-45,6% (62 p) au prezentat fibrilație atrială (FiA) cronica

- la 27,94% (38p) pacienti aflați în RS pe ECG de repaus, s-au decelat la monitorizarea Holter, episoade de FiA paroxistica-57.89% (22 p) precum şi diverse tipuri de aritmie extrasistolica-41.10% (16p). Totodată 36 pacienti (26,4 %) au prezentat BAV de diferite grade, BRS major, tahicardie sinusala, tahicardie paroxistica supraventriculara.

D.p.d.v al FE pacienții au fost încadrați în 3 subclase: 1.cu functie sistolica sever alterata FE<30% (18 bolnavi lot I şi 4 bolnavi lot II); 2 cu functie sistolica moderat alterata FE<40% (72 bolnavi lot I şi 12 bolnavi lot II); 3. cu functie sistolica usor depreciata FE>40% (52 bolnavi lot I şi 12 bolnavi lot II). Repartiția tulburarilor de ritm in funcție de severitatea alterarii fractiei de ejectie a fost următoarea: dintre bolnavii cu EF<30%, 66.66% (18p) au avut FiA, dintre cei cu FE 30-40% , 52.77% (38p)au prezentat FiA, iar 25% (18p) alte tulburări de ritm. Din cei 52 bolnavi cu FE>40% FiA s-a întâlnit numai la 7.69% (4p), iar alte forme de tulburări de ritm la 46.15% (24p).

La 66,6% (36) pacienti cu FiA s-au diagnosticat ecocardigrafic trombi intracavitari (32 barbati si 4 femei). Aceştia au fost prezenți doar la 30% (12) dintre bolnavii aflați în RS, (10 barbati şi 2 femei). Insuficiența mitrală functională de diverse grade s-a diagnosticat la 77,7 % (42)

72% (98) din pacienții lotului I au prezentat din punct de vedere ecocardiografic ecocardiografic unul sau mai mulți dintre următorii parametrii: VS crescut ca dimensiuni, FE scăzută, prezența de trombi intracavitari. În 44% (60 p) din cazuri a fost prezentă o triplă asociere dintre aceste modificări.

Concluzii

1. Prevalența tulburărilor de ritm la bolnavii cu CMD a fost foarte crescută.
2. Aritmia cu prevalența cea mai crescută diagnosticată la bolnavii cu CMD este reprezentată de FiA.

3. Etiologia cea mai frecventă a FiA la pacienţii cu CMD a fost cea ischemică şi toxică.
4. La mai mult de jumătate dintre pacienti cu FiA s-au diagnosticat ecocardigrafic trombi intracavitari.
5. Insuficienţa mitrală functională de diverse grade s-a diagnosticat la peste două treimi dintre bolnavii cu CMD şi FiA.

RELAŢIA DINTRE NIVELUL PLASMATIC AL RECEPTORULUI I SOLUBIL AL FACTORTULUI DE NECROZĂ-α ŞI PREZENŢA FIBRILAŢIEI ATRIALE LA PACIENŢII CU CMD DILATATIVĂ ŞI ICC

Scopul studiului evaluarea rolului unei citokine importante implicate în FiA - receptorul I solubil al TNF-α la pacienţii cu cardiomiopatie dilatativă (CMD) şi insuficienţă cardiacă congestivă (ICC).

Material şi metodă

S-au luat în studiu 54 pacienţi cu ICC internaţi în Clinica Cardiologie-Recuperare, Cluj-Napoca. Diagnosticul de ICC şi CMD s-a pus conform criteriilor Societăţii Europene de Cardiologie [8]. Tuturor pacienţilor li s-a determinat nivelul plasmatic al receptorului I solubil al TNF-α (sTNFR-I) utilizând metoda ELISA (VN-3<pg/ml). Pentru analiza statistică s-a utilizat testul t Student.

Rezultate

Dintre cei 54 pacienţi (p) cu ICC 64,81% bărbaţi (35p) aflaţi în clasa funcţională NYHA III-IV incluşi în studiu, 74,074% (40p) au prezentat etiologie ischemică, iar 25,92% (14p) nonischemică. Fracţia de ejecţie medie a fost de 46,6±39,88%.

Valoarea medie a sTNF-I a fost foarte crescută 222,79±97,08pg/ml, cu o foarte mare variabilitate a acestor valori (cea mai scăzută valoare a fost 26pg/ml, iar valoarea maximă 455,3pg/ml).64,81% (35p) au prezentat fibrilaţie atrială cronică, neexistînd diferenţe în ceea ce priveşte caracteristicile generale ale pacienţilor cu sau fără FiA. Valoarea medie a sTNF-I la pacienţi cu FiA a fost mai scăzută -173,14±43,74pg/ml faţă de pacienţii aflaţi în ritm sinusal (RS) 222,79±97,08pg/ml, fără însă a exista diferenţe semnificative statistic, p=0,45.

Deasemenea nu s-a constatat existenţa unor diferenţe semnificative din punct de vedere statistic nici dacă s-a luat în considerare etiologia ischemică sau nonischemică a ICC, indiferent dacă bolnavii au fost în FiA sau ritm sinusal – tabel I. Trebuie totuşi să remarcăm că pacienţii ischemici au prezentat valori mai crescute decât cei nonischemici, indiferent dacă electrocardiografic au prezentat RS sau FiA.

60% (21p) dintre bolnavii cu FiA au fost diagnosticaţi cu CMD. Caracteristicile acestor pacienţi sunt sumarizate în tabelul II. După cum se poate observa din acest tabel, valorile sTNFR-I au fost mai scăzute la pacienţii cu CMD, fără a existe diferenţe semnificative statistic faţă de cei fără CMD: 211,95±92,22 vs 220,82±15,67pg/ml, p=0,39. Totodată în grupul cu CMD au predominat bărbaţii.

	ICC ischemică	ICC nonischemică	p
FiA	234.70 ±98.26	217.93±94.06	0.32
RS	237.12±112.75	207.04±89.7	0.08
p	0.47	0.49	

Tabel I Valorile sTNFR-I în funcţie de etiologia ICC (pg/ml)

Caracteristici	**FiA cu CMD**	**FiA fără CMD**	**p**
% pacienţi	61% (21)	40% (14)	p = NS
Vârsta medie (ani)	69,4±10,20	70,78±9,18	p = NS
Femei(%)	23,81 (5)	57,14 (8)	p = NS
Bărbaţi (%)	76,19 (16)	42,85 (6)	p = 0.06
FE (%)	37,65±3,065	55,69±6,55	p < 0.0001
STNF-I (pg/ml)	211,95±92	220,82±105,67	p = NS

Tabel II. Caracteristicile pacienţilor cu fibrilaţie atrială

Concluzii

1. Nivelul sTNF-I-α a fost crescut faţă de valorile normale la pacienţii cu ICC, CMD şi fibrilaţie atrială.
2. Valoarea medie a sTNF-I la pacienţi cu FiA a fost mai scăzută faţă de pacienţii aflaţi în ritm sinusal fără însă a exista diferenţe semnificative statistic.
3. Nu au a existat diferenţe semnificative faţă de bolnavii aflaţi în ritm sinusal sau între cei ischemici şi nonischemici.
4. Pacienţii ischemici au prezentat valori mai crescute decât cei nonischemici, indiferent dacă electrocardiografic au prezentat RS sau FiA.
5. sTNFR-I au fost mai scăzute la pacienţii cu CMD, fără a existe diferenţe semnificative statistic faţă de cei fără CMD.

PROFILUL EVOLUTIV AL TULBURARILOR DE RITM LA BOLNAVII CU CMD AFLATI IN TRATAMENT CU AMIODARONA

Scopul studiului-evaluarea evoluţiei bolnavilor cu cardiomiopatie dilatativa care asociaza tulburari de ritm sub tratament antiaritmic cu Amiodarona 200mg/zi.

Material şi metodă. Au fost urmariti pacientii internati in perioada 2003-2004 in Spitalul Clinic de Recuperare-Cardiologie care au fost diagnosticati intr-o prima faza cu insuficienta

cardiaca congestiva (ICC) si ulterior, pe baza examinarilor ecocardiografice au fost inclusi in grupul pacientilor cu cardiomiopatie dilatativa. Tulburarile de ritm pe care o parte dintre acesti pacienti le-au prezentat au fost puse in evidenta atat pe traseul EKG de repaus, cat si la monitorizarile Holter- EKG pe 24 ore. Un procent neinsemnat dintre acestia au avut in antecedente sub aspect terapeutic tratament cu Amiodarona pentru scurte intervale de timp (in special pentru tratamentul in faza acuta a episoadelor de fibrilatie atriala paroxistica). Marea majoritate a pacientilor au beneficiat de initierea tratamentului cu Amiodarona 200 mg/zi in momentul obiectivarii tulburarilor de ritm si au urmat tratamentul sistematic pe toata perioada studiului. In asociere, in functie de situatia particulara a fiecaruia dintre bolnavi, au fost adaugate la schema terapeutică, in special beta-blocante, diuretice, inhibitori ai enzimei de conversie si anticoagulante.

Rezultate. Din totalul de 164 de pacienti cu cardiomiopatie dilatativa la 136 (83%) au fost diagnosticate tulburari de ritm. De departe cea mai frecventa tulburare de ritm intalnita a fost fibrilatia atriala cronica, responsabila in cea mai mare masura si de fenomenele congestive pentru care pacientii s-au adresat serviciului spitalicesc. Asadar au fost 62 pacienti cu FiA cronica (45,6%), 38 pacienti cu ritm sinusal pe EKG de repaus (27.94%), dar cu diverse tulburari ale ritmului cardiac evidentiate la monitorizarea Holter-EKG (FIA paroxistica, aritmie extrasistolica supraventriculara si ventriculara). Diferenta de 36 pacienti, (26,4%) au prezentat anumite tulburari de ritm care au constituit contraindicatii pentru administrarea de Amiodarona (in special datorita efectului bradicardizant). Cele mai frecvente au fost blocurile atrioventriculare si blocul major de ramura stanga. Din punct de vedere al etiologiei cardiomiopatiei dilatative, cea mai frecvent intalnită, a fost cea ischemica (41.41%), urmata indeaproape de cea toxică (33.6%). 25 % dintre pacienți au fost diagnosticați cu CMD idiopatică.

Dintre cei 62 pacienti cu FiA cronica care reprezentau 45,4% din total pacienti, 14 (22.58) beneficiau de tratament cu amiodarona, la acestia s-a adaugat la schema terapeutica una sau mai multe din urmatoarele clase: diuretice, anticoagulante, IECA, beta-blocante, digitalice. Pe parcursul urmaririi pacientilor, care au facut obiectul lucrarii de fata, 48 (35.29%) pacienti au primit suplimentar tratament cu Amiodarona 200 mg/zi dupa o prealabila incarcare. Referitor la incadrarea in clasa functionala NYHA marea majoritate erau incadrati in clasa functionala II, o mica parte in clasa functionala III si restul in clasa functionala I. Stadializarea clasei functionale a fost facuta atat prin testul de efort la cicloergometru sau covor rulant, cat si prin testul de efort cu bratele acolo unde primele 2 modalitati, nu au fost posibile. Astfel, 12 pacienti (19.35%) au fost incadrati in clasa functionala NYHA III in momentul cuprinderii in studiu (au efectuat proba de mers de 6 min.), 44 pacienti (70.76%) in clasa NYHA II (au efectuat test de efort standardizat la cicloergometru sau cu bratele), iar 6 pacienti (9.67%) in NYHA I (au efectuat test de efort standardizat).

La momentul initierii lucrarii de fata 38 (27.94%) pacienti prezentau RS pe EKG de repaus. La acestia s-a adăugat în planul terapeutic Amiodarona, atat ca tratament profilactic (combaterea recurentei episoadelor de Fia paroxistice), cat si curativ (ca urmare a modificarilor inregistrate la monitorizarea Holter- EKG pe 24 ore).

Dintre bolnavii aflați în ritm sinusal, un numar de 5 pacienti (13.15%) au fost incadrati in clasa functionala NYHA III in momentul cuprinderii in studiu (au efectuat proba de mers de 6 min.), 20 pacienti (52.64%) in clasa NYHA II (au efectuat test de

efort standardizat la cicloergometru sau cu bratele), iar 13 (34.21%) pacienti în clasa NYHA I (au efectuat test de efort standardizat).

Tratamentul cu Amiodarona a dus la ameliorarea fractiei de ejectie atat la cei cu FiA cat si la bolnavii cu RS pe traseul de repaus.

De asemenea, a fost evaluat impactul terapiei asupra valorilor parametrilor ecocardiografici, care a cunoscut o imbunatatire la 1 an de tratament, fata de momentul includerii in studiu. Pe langa urmarirea evolutiei dilatarilor cavitatilor cardiace au fost urmarite tot prin aportul ecocardiografiei si unele aspecte patologice, cum ar fi:

- Prezenta trombilor intracavitari
  - -66,6%- 36 pacienti cu FIA prezentau trombi, 32 barbati si 4 femei
  - -30%- 12 pacienti cu RS prezentau trombi 10 barbati si 2 femei
- Prezenta insuficientelor mitrale functionale
  - -77,7%- 42 pacienti cu FIA prezentau insuficienta mitrala grd. II
  - -45%- 18 pacienti cu RS prezentau insuficienta mitrala grd. II
  - -33,3%- 14 pacienti cu tulburari de ritm prezentau insuficienta mitrala grd. II.

Aspectul cel mai important care reiese din monitorizarea de fata este relevant de evolutia favorabila a pacientilor care au beneficiat de tratament antiaritmic, aspect evidentiat prin aportul inregistrarii Holter- EKG pe 24 ore, atat in momentul initial cat si la 1 an de evolutie- figura 1 şi 2.

Avand in vedere ameliorarea semnificativa atat din punct de vedere al simtomatologiei cat si a modificarilor EKG (repaus, Holter 24 ore) putem constata si o imbunatatire semnificativa a clasei functionale, in urma tratamentului careia s-a inglobat si medicatia antiaritmica specifica, amiodarona in cazul de față:

- <u>INITIAL</u>

- 17 pacienti erau incadrati in clasa functionala NYHA III
- 64 pacienti erau incadrati in clasa functionala NYHA II, 42 pacienti prezentand aritmii extrasistolice suplimentare in timpul testului de efort (66%)
- 19 pacienti erau incadrati in clasa functionala NYHA I, 12 pacienti inregistrand in timpul testului de efort modificari extrasistolice (63%)

- <u>LA 1 AN</u>

- 12 pacienti erau incadrati in clasa functionala NYHA III, dar cu imbunatatire de 26% a distantei la proba de mers de 6 min.
- 52 pacienti erau incadrati in clasa functionala NYHA II, 24 prezentau in timpul testului de efort modificari extrasistolice (46%)
- 36 pacienti erau incadrati in clasa functionala NYHA I, 8 pacienti inregistrand modificari aritmice in timpul testului de efort.

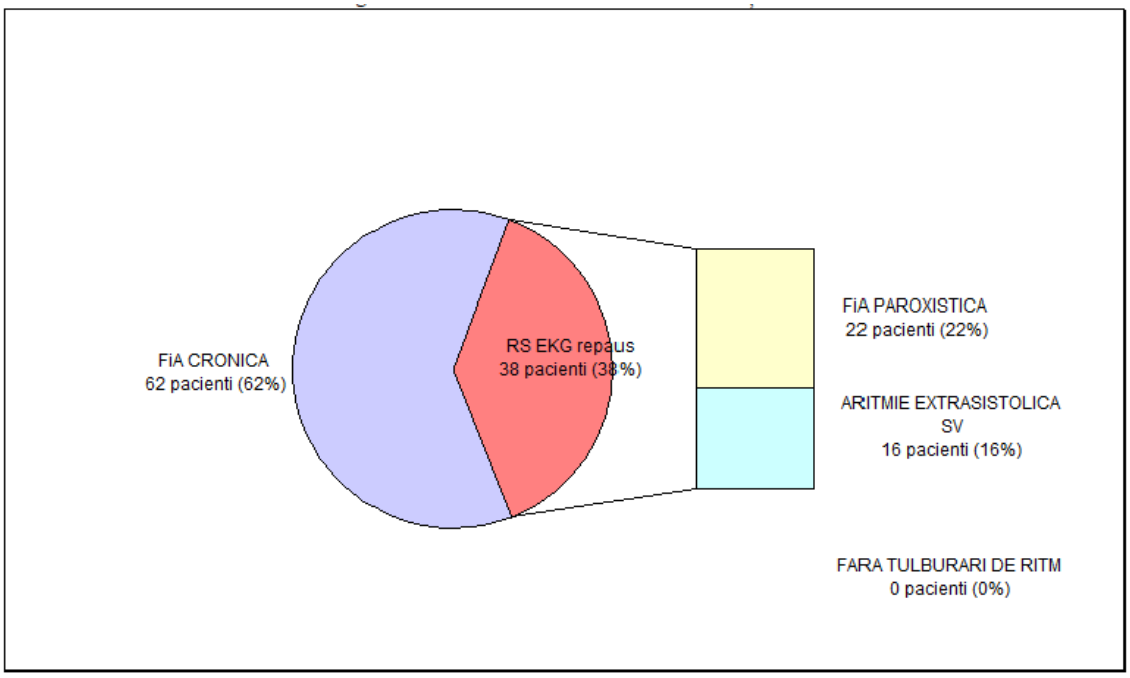

Figura 1-Tulburări de ritm-evaluare inițială

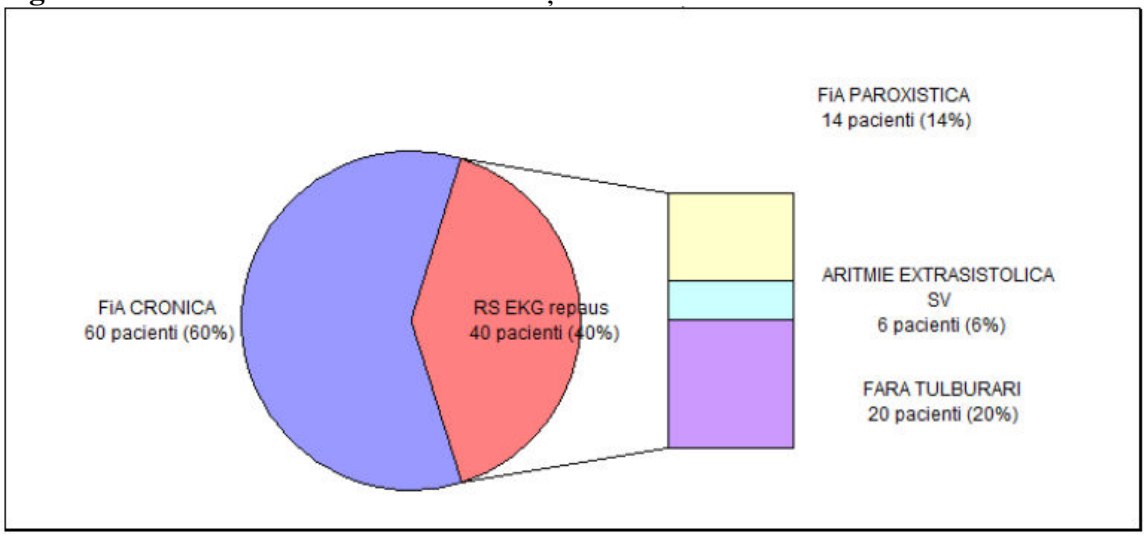

Figura 2-Prezența tulburărilor de ritm la 1 an

Concluzii

1. Prevalenta tulburarilor de ritm la pacientii cu CMD a fost foarte crescuta.
2. Mai mult de jumătate dintre pacientii cu CMD au fost încadrati in clasa functionala NYHA II-IV.
3. Etiologia ischemica si toxica a fost intalnita la majoritatea dintre pacienții cu CMD.
4. Majoritatea pacientilor cu CMD au prezentat inca din momentul diagnosticarii un anumit tip de tulburare de ritm (cel mai frecvent FIA).
5. A existat o interelatie direct proportionala intre dimensiunile VS, prezenta trombilor intracavitari, scaderea FE a VS cu aparitia tulburarilor de ritm
6. Amiodarona s-a dovedit a avea efecte benefice in special asupra imbunatatirii fractiei de ejectie si intr-o mai mica masura asupra dimensiunilor cardiace.

ROLUL INHIBITORILOR SISTEMULUI RENINA ANGIOTENSINĂ-ALDOSTERON ÎN TRATAMENTUL FIBRILȚIEI ATRIALE DIN CMD COMPLICATA CU INUFICIENȚA CARDIACĂ CONGESTIVĂ

INTRODUCERE

Scopul studiului- determinarea genotipurilor M235T şi T174 al angiotensinogenului, I/D a EC, respectiv A1166C a receptorilor AT1 ai AGII la pacienții cu ICC aflați în FiA, precum şi proporția de pacienți cu aceste mutații patogene care au primit ca medicație IECA, respectiv sartani.

Material si metodă: S-au luat în studiu 47 de subiecți, dintre care 25 pacienți cu CMD şi ICC clasa funcțională NYHA III-IV, internați în Clinica de Cardiologie-Recuperare din Cluj – Napoca şi 22 subiecți fără patologie cardiovasculară (martori).

Studiul utilizat in cadrul acestui grup de pacienți este unul observațional, analitic, retrospectiv bazat pe analiza datelor din foaia de observație. Insuficiența cardiacă a fost definită conform criteriilor recomandate de Societatea Europeana de Cardiologie.

Tuturor pacientilor li s-au detreminat glicemia şi fractiunile lipidice, valoarea fragmentului BNP (8-29), radiografie toracică - pentru determinarea indicele cardio-toracic, precum şi determinări ecocardiografie.

Determinarea mutațiilor genetice s-a realizat utilizând metoda PCR (reacție de polimerizare in lanț).

Rezultate:

Etiologia ischemică a CMD a fost prezentă la 17 pacienți (68%), iar restul de 8 (32%) au prezentat etiologie idioptaică sau etanolică. Prezența tulburarilor de ritm **-**18 p (72 %) au fost diagnosticați cu tulburari de ritm, după cum urmează: fibrilație atrială- 15 p (60%), extrasistolie ventriculară-3p (15,78 %).

Distributia in functie de mutatia M235T AGT

- 8 pacienti (32 %) -negativ MM
- 11 pacienti (44 %) - heterozigoti MT
- 6 pacienti (24 %) - homozigoti TT

Distributia in functie de mutatia T174M AGT

- 22 pacienti (88 %)erau negativ TT
- 3 pacienti (12 %)erau heterozigoti TM

Distributia in functie de mutatia I/D a ACE

- 9 pacienti (36 %)erau homozigoti DD
- 6 pacienti (24 %)erau negativi II
- 10 pacienti (40 %)erau heterozigoti I/D

Distributia in functie de mutatia A1166CAGTR1

- 15 pacienti (60 %)erau negativ AA
- 7 pacienti (28 %)erau heterozigoti AC
- 3 pacienti (12 %)erau homozigoti CC

S-au găsit decelat următoarele asocieri ale polimorfismului genetic:

- 3 pacienți au prezentat asociate două mutații cu risc:

→1 pacient: Homozigot TT(M235T AGT) şi Homozigot CC(A1166C AGTR)

→2 pacienți: Homozigot TT(M235T AGT) şi Homozigot DD(I/D ACE)

Nici un pacient nu prezenta asociat 3sau 4 mutații cu risc.

Distribuția mutațiilor genetice la pacienții cu fibrilație atrială, precum şi tratmentul cu inhibitori ai enzimei de conversie (IECA) sau sartani este sintetizată în tabelul III.

M235T	T174M	ACE DEL/INS	AT1	IECA	SARTAN
HETEROZIGOT MT	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	DA	NU
NEGATIV MM	NEGATIV TT	NEGATIV II	HETEROZIGOT AC	DA	NU
HOMOZIGOT TT	NEGATIV TT	NEGATIV II	NEGATIV AA	DA	NU
HOMOZIGOT TT	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	DA	NU
HETEROZIGOT MT	NEGATIV TT	NEGATIV II	NEGATIV AA	DA	NU
NEGATIV MM	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	DA	NU
HOMOZIGOT TT	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	NU	DA
HETEROZIGOT MT	NEGATIV TT	NEGATIV II	NEGATIV AA	NU	DA
HOMOZIGOT TT	NEGATIV TT	HETEROZIGOT I/D	HETEROZIGOT AC	DA	NU
HETEROZIGOT MT	NEGATIV TT	NEGATIV II	HOMOZIGOT CC	NU	NU
HETEROZIGOT MT	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	NU	NU
NEGATIV MM	NEGATIV TT	HOMOZIGOT DD	NEGATIV AA	NU	DA
HETEROZIGOT MT	HETEROZIGOT TM	HETEROZIGOT I/D	NEGATIV AA	DA	NU
HETEROZIGOT MT	NEGATIV TT	HETEROZIGOT I/D	NEGATIV AA	DA	NU
NEGATIV MM	NEGATIV TT	HETEROZIGOT I/D	HOMOZIGOT CC	DA	NU

Tabelul III- Distribuția mutațiilor genetice la pacienții cu fibrilație atrială, precum şi tratamentul cu IECA sau sartani

Din analiza datelor tabelului III se pot observa următoarele:

POLIMORFISMUL GENETIC DE LA NIVELUL ANGIOTENSINOGENULUI

Mutația M235T cu potențial patogen (heteroZIGOT MT sau homozigot TT) este prezentă la 73,33 % (11) din pacienții cu fibrilație atrială.

Mutația T174M –un singur pacient cu FiA prezintă formă potențial patogenă, respectiv, heterozigot TM.

COMBINAȚII dintre cele două forme de mutații ale AGT : un singur pacient : heterozigot MT+heterozigot TM.

POLIMORFISMUL GENETIC DE LA NIVELUL ENZIMEI DE CONVERSIE

Formele potențial patogene ale EC (homozigot DD sau heterozigot I/D)-66,66% (10 pacienți).

POLIMORFISMUL GENETIC DE LA NIVELUL RECEPTORULUI AT1 AL AG II

Formele potențial patogene (hetrozigot AC sau homozigot CC): 26,66% (4 pacienți).

ASOCIAȚII DINTRE POLIMORFISMUL GENETIC DE LA NIVELUL ENZIMEI DE CONVERSIE ŞI A RECEPTORULUI AT1:

-heterozigot I/D+heterozigot AC-1 pacient

-heterozigot I/D+homozigot CC-1 pacient

ASOCIAȚII DINTRE ALTE MUTAȚII GENETICE**:**

În studiul de față aceste asocieri au fost prezente în procente scăzute: ACE D/D+ haplotip AGT-13,33%, ACE I/D+ haplotip AGT =6,66%, ACE I/D-AT_1RA 1166 şi haplotip AGT-6,66%.

IECA au fost administrați la 66,66% (10 p) dintre pacienții cu FiA, toți prezentand asocieri patogene de mutații genetice.

Sartanii au fost adminstrați doar la 20% (3p) dintre bolnavii cu FiA, niciunul cu asocieri patologice ale polimorfismului genetic.

13,33% dintre pacienții aflați în FiA nu au beneficiat de tratment cu IECA sau sartani.

Concluzii

1. Polimorfismul genetic al SRAA poate fi implicat în apariția fibrilației atriale la pacienții cu CMD şi insuficiență cardiacă.
2. Prezența mutațiilor genetice patogene în randul martorilor s-a înregistrat în special la subiecții cu obezitate, rezultate punând în discuție rolul SRAA în patogeneza obezității, prin intermediul probabil a modificării rezistenței la insulină.
3. Inhibarea SRAA (prin utilizarea IECA sau a sartanilor) poate fi responsabilă de prevenirea apariției fibrilației atriale la pacienții cu insuficiență cardiacă

Concluzii generale

1. Prevalența tulburărilor de ritm la bolnavii cu CMD a fost foarte crescută.
2. Mai mult de jumătate dintre pacientii cu CMD au fost încadrati in clasa functionala NYHA II-IV.
3. Aritmia cu prevalența cea mai mare diagnosticată la bolnavii cu CMD este reprezentată de FiA.
4. Etiologia cea mai frecventă a FiA la pacienții cu CMD a fost cea ischemică şi toxică.
5. La mai mult de jumătate dintre pacienti cu FiA s-au diagnosticat ecocardigrafic trombi intracavitari.
6. Insuficiența mitrală functională de diverse grade s-a diagnosticat la peste două treimi dintre bolnavii cu CMD şi FiA.
7. A existat o interelatie direct proportionala intre dimensiunile VS, prezenta trombilor intracavitari, scaderea FE a VS şi aparitia tulburarilor de ritm
8. Amiodarona s-a dovedit a avea efecte benefice in special asupra imbunatatirii fractiei de ejectie si intr-o mai mica masura asupra dimensiunilor cardiace.
9. Polimorfismul genetic al SRAA poate fi implicat în apariția fibrilației atriale la pacienții cu CMD şi insuficiență cardiacă.
10. Prezența mutațiilor genetice patogene în randul martorilor s-a înregistrat în special la subiecții cu obezitate, rezultate punând în discuție rolul SRAA în patogeneza obezității, prin intermediul probabil a modificării rezistenței la insulină.
11. Inhibarea SRAA (prin utilizarea IECA sau a sartanilor) poate fi responsabilă de prevenirea apariției fibrilației atriale la pacienții cu insuficiență cardiacă
12. Nivelul sTNF-I-α a fost crescut față de valorile normale la pacienții cu ICC, CMD şi fibrilație atrială.
13. Valoarea medie a sTNF-I la pacienți cu FiA a fost mai scăzută față de pacienții aflați în ritm sinusal fără însă a exista diferențe semnificative statistic.
14. Pacienții ischemici au prezentat valori mai crescute a sTNF-I decât cei nonischemici, indiferent dacă electrocardiografic au prezentat RS sau FiA.
15. sTNFR-I au fost mai scăzute la pacienții cu CMD, fără a existe diferențe semnificative statistic față de cei fără CMD.
16. Un rol important în tratamentul pacienților cu CMD şi FiA l-ar putea avea medicația cu acțiuni dovedite antiinflamatorii (IECA, sartanii, antialdosteronicele, statinele şi activatorii receptorilor PPRγ).

Contribuţii personale

Dintre contribuţiile originale ale tezei menţionăm:

1.Realizarea unui profilul evolutiv (timp de 1 an) al bolnavilor cu FiA şi CMD aflaţi sub tratment cu amiodaronă .

2. Evaluarea rolului sTNF-I în patogeneza FiA la şia insuficienţiei cardiace.

3. Analiza posibilului rol al polimorfismul genetic al SRAA în apariţia fibrilaţiei atriale la pacienţii cu CMD şi insuficienţă cardiacă. În acest context inhibarea SRAA (prin utilizarea IECA sau a sartanilor) poate fi responsabilă de prevenirea apariţiei fibrilaţiei atriale la pacienţii cu insuficienţă cardiacă

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DOCTORAL THESIS ABSTRACT

DYSRHYTHMIAS IN DILATED CARDIOMYOPATHIES DIAGNOSIS, TREATMENT AND DEVELOPMENT OUTLINE

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Diverse, rather underestimating epidemiological studies report approximately 20/100000/year incidence and 38/100000/year prevalence for dilated cardiomyopathy. Dilated cardiomyopathy ranks third among etiological causes of heart failure and is the first cause of cardiac transplantation.

Despite improved heart failure treatment, dilated cardiomyopathy remains an important cause of cardiovascular mortality, by rhythm disorder mainly. AF is the most frequent arrhythmia in HF. Its onset may lead to aggravated symptoms, higher risk for thromboembolic complications and carries a more severe long-term prognosis.

Consequently, this paper is based on the assumption of ever- growing heart failure incidence and the closely related increase of newly diagnosed cases of dilated cardiomyopathy. The discovery of novel efficient medication in heart failure treatment has led to the improvement of patient survival rate, however it also elevated rhythm disorders incidence in such patients. The prognosis remains unfavorable especially in patients in whom dilated cardiomyopathy associates with congestive heart failure.

The **theoretical** part of the paper assesses the main forms of cardiomyopathy, with special focus on dilated cardiomyopathy, further providing an overview of the mechanisms involved by dilated cardiomyopathy as well as heart failure pathogeneses. Moreover, all forms of arrhythmias that may represent complications of dilated cardiomyopathy were analyzed from both pathogenesis and possible therapies viewpoints.

The special part includes several research approaches. We examined firstly the development outline of patients with dilated cardiomyopathy and rhythm disorders under treatment with amiodarone and secondly, the incidence of atrial fibrillation, by far the most frequent arrhythmia found in heart failure. The next two chapters investigate the possible relation between the plasma level of the tumor necrosis factor - I soluble receptor and the presence of atrial fibrillation, as well as the angiotensin-aldorestone system inhibitors role in the treatment of atrial fibrillation in dilated cardiomyopathy complicated with congestive heart failure.

ATRIAL FIBRILLATION INCIDENCE IN PATIENTS WITH DILATED CARDIOMYOPATHY

Aim of the study: assessment of atrial fibrillation prevalence (AF) in DCM patients admitted with the Clinic of Cardiology and Recovery of Cluj- Napoca.

Material and method: A number of 164 patients divided in two groups were considered: group I - 136 patients with rhythm disorders and group II - 28 patients with DCM without rhythm disorders. In group I, we analyzed rhythm disorder types, the recommended antiarrhythmic medication as well as the two groups comparative characteristics from age, gender, cardiovascular risk factors, CHF etiology, ECG and echocardiographic parameters, ECG Holter/24h monitor viewpoints.

Outcome: The prevalence of rhythm disorders in the 470 patients with CHF was 82.9%.

In group I, the DCM etiology was ischemic in 33.6 % (46) patients, toxic in 41.4 % (56), respectively idiopathic in 25% (34) of the patients. In group II, the DCM etiology was as follows: ischemic in 28.2 % (8) patients, toxic in 14.8 % (4), respectively idiopathic in 57% (16) of the patients. 76% of the patients were monitored by ECG Holter/24h.

The ischemic etiology was identified in 66.4% of the patients with rhythm disorders existent in the treatment of DCM diagnosis.

Upon the analysis of rhythm disorders in group I as evidenced by resting ECG and Holter-ECG/24h, the following were noted:

- 45.6% (62 p) exhibited chronic atrial fibrillation (AF)

- in 27.94% (38p) patients in SR on resting ECG, Holter monitoring evidenced episodes of paroxysmal AF - 57.89% (22 p) as well as various types of extrasystolic arrhythmia - 41.10% (16p). Concurrently, 36 patients (26.4 %) had various degrees of AV block, major LBBB, sinus tachycardia and paroxysmal supraventricular tachycardia.

From EF standpoint, the patients were framed in 3 subclasses: 1. with severely altered systolic function EF<30% (18 patients in group I and 4 patients in group II); 2. with moderately altered systolic function EF<40% (72 patients in group I and 12 patients in group II); 3. with mildly depressed systolic function EF>40% (52 patients in group I and 12 patients in group II). The distribution of rhythm disorders according to the severity of ejection fraction alteration was the following: among patients with EF<30%, 66.66% (18p) showed AF, among those with EF 30-40%, 52.77% (38p) had AF and 25% (18p) exhibited other rhythm disorders. Among the 52 patients with EF>40%, AF was found only in 7.69% (4p), while other forms of rhythm disorders were reported in 46.15% (24p).

Echocardiographically, intracavitary thrombi were diagnosed in 66.6% (36) patients with AF (32 men and 4 women). They were present only in 30% (12) of the patients with SR (10 men and 2 women). Functional mitral regurgitation of various degrees was diagnosed in 77.7 % (42 p).

72% (98) of the patients in group I presented echocardiographically one or several parameters: enlarged LV, low EF, intracavitary thrombi. In 44% (60 p) of the cases, threefold association of such changes was found.

Conclusions:

1. The prevalence of rhythm disorders in DCM patients was very high.
2. The highest prevalence arrhythmia diagnosed in DCM patients is represented by AF.
3. The most frequent AF etiology in DCM patients was ischemic and toxic.
4. In more than half of the patients with AF, intracavitary thrombi were diagnosed echocardiographically.
5. Functional mitral regurgitation of various degrees was diagnosed in over two thirds of DCM and AF patients.

THE RELATION BETWEEN THE PLASMA LEVEL OF NECROSIS FACTOR-α I - SOLUBLE RECEPTOR AND ATRIAL FIBRILLATION PRESENCE IN PATIENTS WITH DCM AND CHF

Aim of the study: assessment of the role of an important cytokine involved in AF – TNF-α I soluble receptor in patients with dilated cardiomyopathy (DCM) and congestive heart failure (CHF).

Material and method: The study considered 54 patients with CHF admitted in the Clinic of Cardiology-Recovery of Cluj-Napoca. The CHF and DCM diagnosis was placed according to the European Society of Cardiology criteria [8]. In all patients, the plasma level of TNF-α (sTNFR-I) - I soluble receptor was determined based on ELISA (VN-3<pg/ml) technique. For statistical analysis, the Student's t-test was used.

Outcome: Of the 54 patients (p) with CHF 64.81% men (35p) included in NYHA III-IV functional class, 74.074% (40p) had ischemic and 25.92% (14p) nonischemic etiologies. The average ejection fraction was 46.6±39.88%.

The mean value of sTNF-I was very high, 222.79±97.08pg/ml, with high variability of values (the lowest value was 26pg/ml, while the maximum value was 455.3pg/ml). 64.81% (35p) had chronic atrial fibrillation, without differences related to the general features of the patients with or without AF. The mean value of sTNF-I in patients with AF was lower, -173.14±43.74pg/ml compared to the patients in sinus rhythm (SR) 222.79±97.08pg/ml, however without statistically significant differences, p=0.45.

Additionally, statistically significant differences were neither reported in ischemic nor in nonischemic CHF etiology, regardless if patients were in AF or sinus rhythm – table I. We should however note that the values of ischemic patients were higher than those of nonischemic patients, irrespective if electrocardiographically, SR or AF were reported.

60% (21p) of the patients with AF were diagnosed with DCM. The features specific to these patients are summarized in table II. This table shows that sTNFR-I values were lower in DCM patients, without statistically significant differences compared to patients without DCM: 211.95±92.22 vs. 220.82±15.67pg/ml, p=0.39. Concurrently, in the DCM group, men were predominant.

	ICC ischemică	ICC nonischemică	p
FiA	234.70 ±98.26	217.93±94.06	0.32
RS	237.12±112.75	207.04±89.7	0.08
p	0.47	0.49	

Table I sTNFR-I values according to CHF etiology (pg/ml)

Caracteristici	FiA cu CMD	FiA fără CMD	p
% pacienţi	61% (21)	40% (14)	p = NS
Vârsta medie (ani)	69,4±10,20	70,78±9,18	p = NS
Femei(%)	23,81 (5)	57,14 (8)	p = NS
Bărbaţi (%)	76,19 (16)	42,85 (6)	p = 0.06
FE (%)	37,65±3,065	55,69±6,55	p < 0.0001
STNF-I (pg/ml)	211,95±92	220,82±105,67	p = NS

Table II. Features of atrial fibrillation patients

Conclusions:

1. sTNF-I-α was elevated compared to normal values in patients with CHF, DCM and atrial fibrillation.
2. sTNF-I mean value in patients with AF was lower compared to the patients with sinus rhythm, however there were no statistically significant differences.
3. No significant differences compared to the patients with sinus rhythm or between ischmic and nonischemic patients were found.
4. Values in ischemic patients were higher than in nonischemic patients, regardless if SR or AF were reported electrocardiographically.
5. sTNFR-I were lower in patients with DCM, without statistically significant differences compared to those without DCM.

THE DEVELOPMENT OUTLINE OF RHYTHM DISORDERS IN PATIENTS WITH DCM UNDER TREATMENT WITH AMIODARONE

Aim of the study: assessment of development in patients with dilated cardiomyopathy associated with rhythm disorders, under antiarrhythmic treatment with amiodarone 200mg/day.

Material and method: we monitored the patients admitted during 2003-2004 in the Clinic of Cardiology-Recovery, who were primarily diagnosed with congestive heart failure

(CHF) and who were included subsequently, based on echocardiographic examinations, in the group of patients with dilated cardiomyopathy. Rhythm disorders, which part of the patients presented, were confirmed both on resting ECG tracing, as well as by Holter-ECG/24h monitoring. The therapy history of an insignificant percentage of the patients included treatment with amiodarone for short periods of time (especially for the treatment of paroxysmal atrial fibrillation episodes in the acute stage). Most of the patients initiated treatment with amiodarone 200 mg/day upon the presentation of rhythm disorders and were under systematic treatment over the entire study period. According to the peculiar situation of each patient, the therapy scheme included in association especially beta-blockers, diuretics, conversion enzyme inhibitors and anticoagulants.

Outcome: Of the total of 164 patients with dilated cardiomyopathy, rhythm disorders were diagnosed in 136 (83%). By far, the most frequent rhythm disorder encountered was the chronic atrial fibrillation, responsible to a great extent also for the congestive events for which the patients sought hospital care. Therefore, there were 62 patients with chronic AF (45.6%), 38 patients with sinus rhythm on resting ECG (27.94%), however with various disorders of heart rhythm recorded upon Holter-ECG monitoring (paroxysmal AF, supraventricular and ventricular extrasystolic arrhythmia). The remaining 36 patients, (26.4%) presented certain rhythm disorders, which constituted contraindication for amiodarone administration (especially due to bradycardia effect). Among, the most frequent were the atrioventricular blocks and the major left bundle branch block. From dilated cardiomyopathy etiology viewpoint, the most frequently identified was ischemic (41.41%), closely followed by toxic (33.6%). 25 % of the patients were diagnosed with idiopathic DCM.

Of the 62 patients with chronic AF representing 45.4% of total patients, 14 (22.58) were under treatment with amiodarone. Their therapy scheme was supplemented by one or several of the following classes: diuretics, anticoagulants, ACE inhibitors, beta-blockers and digitalis. During the monitoring of the patients object of the paper herein, 48 (35.29%) additionally received treatment with amiodarone 200 mg/day subsequent a prior loading dose. Most of the patients were framed in the NYHA II functional class, a few in NYHA III functional class and the rest in NYHA I functional class. The functional class was assigned in accordance to both exercise stress testing by cycloergometer or

treadmill, as well as by arm ergometer where the first two options were impossible. Thus, 12 patients (19.35%) were framed in NYHA III functional class at the time of inclusion in the study (performed the six-minute walk test), 44 patients (70.76%) in NYHA II class (performed a standard exercise stress testing by cycloergometer or arm ergometer), and 6 patients (9.67%) in NYHA I (performed a standard exercise stress testing).

At the time of initiation of this paper, 38 (27.94%) of the patients were in SR on resting ECG. Their therapy plan was supplemented by amiodarone, both prophylactically (recurrence control of paroxysmal AF episodes), as well as curatively (subsequent changes reported by Holter- ECG 24h monitoring).

Among the patients with sinus rhythm, a number of 5 patients (13.15%) were framed in NYHA III functional class at the time of inclusion in the study (performed the six-minute walk test), 20 patients (52.64%) were framed in class NYHA II (performed a standard exercise stress testing by cycloergometer or arm ergometer), while 13 (34.21%) patients in class NYHA I (performed a standard exercise stress testing).

The treatment with amiodarone led to the improvement of the ejection fraction both in patients with AF as well as in patients with SR on resting tracing.

Moreover, we assessed the therapy impact over echocardiographic parameter values, which improved within one year from treatment compared to the moment of inclusion in the study. Beside monitoring dilation development of heart chambers, certain pathological aspects were also investigated echocardiographically, i.e.:

- Presence of intracavitary thrombi.

-66.6% - 36 patients with AF exhibited thrombi, 32 men and 4 women.

-30% - 12 patients with SR had thrombi, 10 men and 2 women.

- Presence of functional mitral regurgitation.

-77.7% - 42 patients with AF developed II degree mitral failure.

-45% - 18 patients with SR developed II degree mitral failure.

-33.3% - 14 patients with rhythm disorders developed II degree mitral failure.

The most important aspect resulting from this monitoring is the favorable evolution of the patients who benefited of antiarrhythmic treatment, as evidenced by Holter - ECG 24h recording, both initially as well as within one year of evolution – figure 1 and 2.

Given the significant symptomatological improvement as well as ECG changes (resting ECG, Holter 24h) we also noted a considerable improvement of the functional class, since treatment was supplemented by specific antiarrhythmic medication, i.e amiodarone:

- INITIALLY

- 17 patients were framed in NYHA III functional class.
- 64 patients were framed in NYHA II functional class, 42 patients presenting additional extrasystolic arrhythmias during exercise stress testing (66%).
- 19 patients were framed in NYHA I functional class, 12 patients registering extrasystolic changes during exercise stress testing (63%).

- WITHIN 1 YEAR

- 12 patients were framed in NYHA III functional class, however with 26% distance improvement of the six-minute walk test.
- 52 patients were framed in NYHA II functional class, in 24 p. extrasystolic changes were reported during exercise stress testing (46%).
- 36 patients were framed in NYHA I functional class, 8 patients registering arrhythmic changes during exercise stress testing.

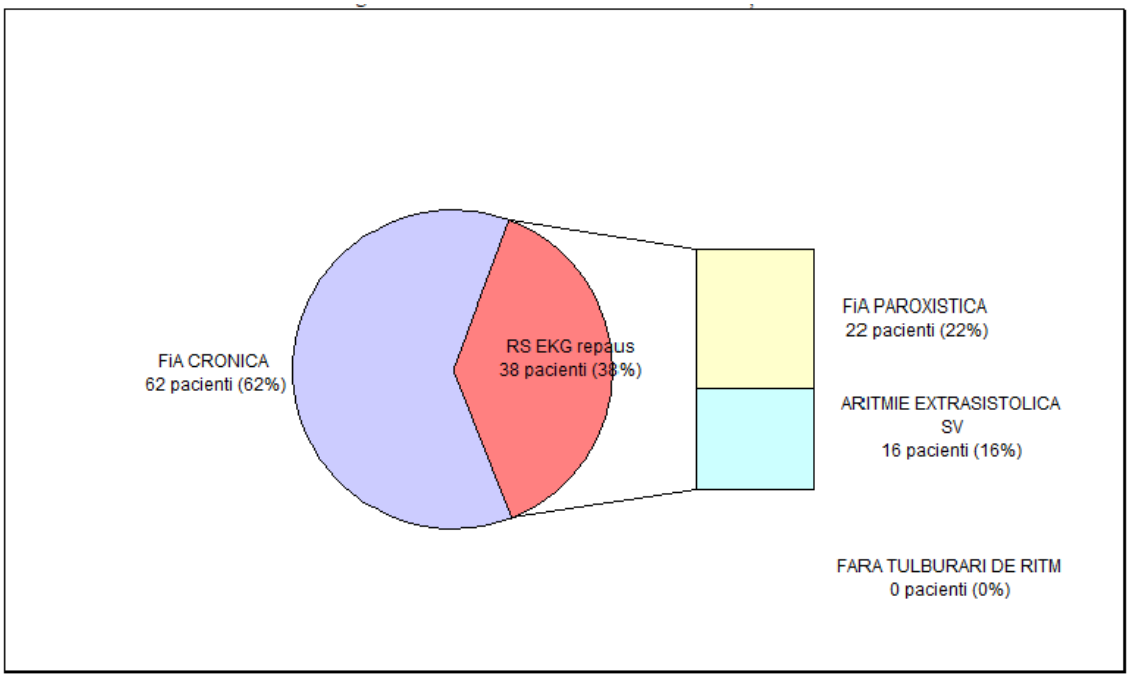

Figure 1 – Rhythm disorders – initial assessment

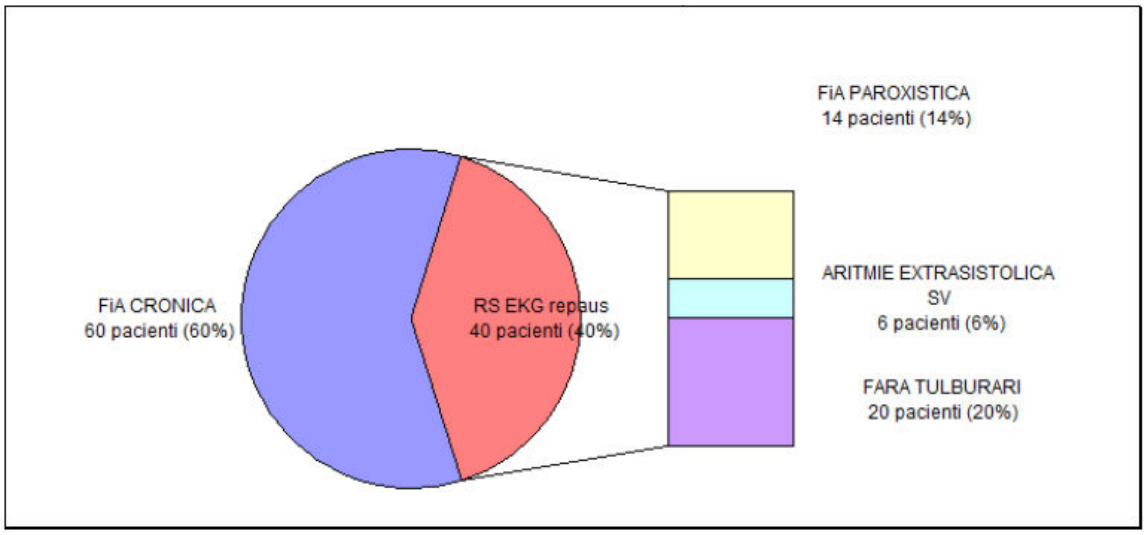

Figure 2 – Presence of rhythm disorders within 1 year

Conclusions

1. Prevalence of rhythm disorders in DCM patients was very high.
2. More than half of DCM patients were framed in NYHA II-IV functional class.
3. The ischemic and toxic etiology was found in the majority of DCM patients.
4. Most of the patients with DCM exhibited as early as the diagnosis moment a certain rhythm disorder type (most frequently, AF).
5. There was a directly proportional interrelation between LV sizes, intracavitary thrombi presence, low LVEF and rhythm disorders emergence.
6. Amiodarone proved beneficial especially by improving the ejection fraction and had little impact over heart sizes.

THE ROLE OF RENIN ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS IN THE TREATMENT OF ATRIAL FIBRILLATION IN DCM COMPLICATED BY CONGESTIVE HEART FAILURE

Aim of the study: establishment of M235T and T174 angiotensinogen genotypes, CE I/D, respectively A1166C of AGII AT1 receptors in patients with CHF in AF, as well as the proportion of patients with such pathogenic mutations who received ACE inhibitor medication, respectively sartans.

Material and method: The study was carried out on 47 subjects, of whom 25 were patients with DCM and CHF NYHA III-IV functional class, admitted with the Clinic of Cardiology and Recovery of Cluj –Napoca and 22 subjects without cardiovascular pathology (control group).

The study was observational, analytical, retrospective and based on the analysis of data from consultation sheets. Heart failure was defined according to the criteria recommended by the European Society of Cardiology. Blood glucose and lipid fraction levels and BNP fragment (8-29) values were determined in all patients, chest x-rays, in order to establish the cardiothoracic index as well as echocardiographical examinations were performed.

Determination of genetic mutations was carried out by PCR method (polymerase chain reaction).

Outcome: The ischemic etiology of the DCM was present in 17 patients (68%), while the remaining 8 (32%) presented an idiopathic or ethanol etiology. The presence of rhythm disorders **-**18 p (72 %) were diagnosed with rhythm disorders, as follows: atrial fibrillation - 15 p (60%), ventricular extrasystole - 3p (15.78 %).

Distribution according to AGT M235T mutation

- 8 patients (32 %) - negative MM
- 11 patients (44 %) - heterozygote MT
- 6 patients (24 %) - homozygote TT

Distribution according to AGT T174M mutation

- 22 patients (88 %) were negative TT
- 3 patients (12 %) were heterozygote TM

Distribution according to I/D ACE mutation

- 9 patients (36 %) were homozygote DD
- 6 patients (24 %) were negative II
- 10 patients (40 %) were heterozygote I/D

Distribution according to A1166CAGTR1 mutation

- 15 patients (60 %) were negative AA
- 7 patients (28 %) were heterozygote AC
- 3 patients (12 %) were homozygote CC

The following associations of genetic polymorphism were established:

- 3 patients presented two associated risk mutations:

→1 patient: Homozygote TT (AGT M235T) and Homozygote CC (AGTR A1166C)

→2 patients: Homozygote TT (AGT M235T) and Homozygote DD (I/D ACE)

No patient presented associated 3 or 4 risk mutations.

The distribution of genetic mutations in patients with atrial fibrillation as well as the treatment with conversion enzyme inhibitors (ACE inhibitors) or sartans is synthesized in table III.

M235T	T174M	ACE DEL/INS	AT1	ACEI	SARTANS
HETEROZYGOTE MT	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	YES	NO
NEGATIVE MM	NEGATIVE TT	NEGATIVE II	HETEROZYGOTE AC	YES	NO
HOMOZYGOTE TT	NEGATIVE TT	NEGATIVE II	NEGATIVE AA	YES	NO
HOMOZYGOTE TT	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	YES	NO
HETEROZYGOTE MT	NEGATIVE TT	NEGATIVE II	NEGATIVE AA	YES	NO
NEGATIVE MM	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	YES	NO
HOMOZEGOTE TT	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	NO	YES
HETEROZYGOTE MT	NEGATIVE TT	NEGATIVE II	NEGATIVE AA	NO	YES
HOMOZYGOTE TT	NEGATIVE TT	HETEROZYGOTE I/D	HETEROZYGOTE AC	YES	NO
HETEROZYGOTE MT	NEGATIVE TT	NEGATIVE II	HOMOZYGOTE CC	NO	NO
HETEROZYGOTE MT	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	NO	NO
NEGATIVE MM	NEGATIVE TT	HOMOZYGOTE DD	NEGATIVE AA	NO	YES
HETEROZYGOTE MT	HETEROZYGOTE TM	HETEROZYGOTE I/D	NEGATIVE AA	YES	NO
HETEROZYGOTE MT	NEGATIVE TT	HETEROZYGOTE I/D	NEGATIVE AA	YES	NO
NEGATIVE MM	NEGATIVE TT	HETEROZYGOTE I/D	HOMOZYGOTE CC	YES	NO

Table III- Distribution of genetic mutations in patients with atrial fibrillation as well as the treatment with ACE inhibitors or sartans

The following ensue from the analysis of the data in table III:

GENETIC POLYMORPHISM AT ANGIOTENSINOGEN LEVEL

M235T mutation with pathogenic potential (heterozygote MT or homozygote TT) is present in 73.33 % (11) of the patients with atrial fibrillation.

T174M mutation – a single patient with AF has a potentially pathogenic form, heterozygote TM, respectively.

COMBINATIONS between the two forms of AGT mutations: a single patient: heterozygote MT + heterozygote TM.

GENETIC POLYMORPHISM AT CONVERSION ENZYME LEVEL

Potentially pathogenic CE forms (homozygote DD or heterozygote I/D)-66.66% (10 patients).

GENETIC POLYMORPHISM AT AG II OF AT1 RECEPTOR LEVEL

Potentially pathogenic forms (heterozygote AC or homozygote CC): 26.66% (4 patients).

ASSOCIATIONS BETWEEN GENETIC POLIMORPHYSM AT CONVERSION ENZYME LEVEL AND AT1 RECEPTOR:

-heterozygote I/D + heterozygote AC-1 patient

-heterozygote I/D + homozygote CC-1 patient

ASSOCIATIONS AMONG OTHER GENETIC MUTATIONS**:**

In this study, such associations were present in low percentages: ACE D/D + AGT haplotype -13.33%, ACE I/D + AGT haplotype = 6.66%, ACE I/D-AT_1RA 1166 and AGT haplotype -6.66%.

ACE inhibitors were administered in 66.66% (10 p) of AF patients, all presenting pathogenic associations of genetic mutations.

Sartans were administered in only 20% (3p) of AF patients, none with pathological associations of genetic polymorphism.

13.33% of the patients with AF did not benefit of treatment with ACE inhibitors or sartans.

Conclusions

1. RAAS genetic polymorphism may be involved in the emergence of atrial fibrillation in DCM and heart failure patients.
2. The presence of pathogenic genetic mutations among the control group was reported especially in obese patients, results which question RAAS role in obesity pathogenesis via most likely changes to insulin resistance.

3. RAAS inhibition (by use of ACE inhibitors or sartans) may be responsible for prevention of atrial fibrillation emergence in heart failure patients.

General conclusions

1. Prevalence of rhythm disorders in DCM patients was very high.
2. More than half of DCM patients were framed in NYHA II-IV functional class.
3. Most prevalent arrhythmia diagnosed in DCM patients is represented by AF.
4. Most frequent etiology of AF in DCM patients was ischemic and toxic.
5. In more than a half of the AF patients, intracavitary thrombi were diagnosed echocardiographically.
6. Functional mitral regurgitation of various degrees was diagnosed in over two thirds of DCM and AF patients.
7. There is directly proportional interrelation between LV sizes, intracavitary thrombi presence, low LVEF and rhythm disorders emergence.
8. Amiodarone proved beneficial especially by improving ejection fraction and had little impact over heart sizes.
9. RAAS genetic polymorphism may be involved in the onset of atrial fibrillation in DCM and heart failure patients.
10. The presence of pathogenic genetic mutations among the control group was reported especially in obese patients, results which question RAAS role in obesity pathogenesis via most likely changes in insulin resistance.
11. RAAS inhibition (by use of ACE inhibitors or sartans) may be liable for prevention of atrial fibrillation emergence in heart failure patients.
12. sTNF-I-α level was elevated compared to normal values in patients with CHF, DCM and atrial fibrillation.
13. sTNF-I average value in patients with AF was lower compared to patients with sinus rhytm without statistically significant differences.
14. In ischemic patients, sTNF-I values were elevated compared to non-ischemic patients, irrespective if SR of AF were present electrocardiographically.
15. sTNFR-I were lower in patients with DCM, without statistically significant difference compared to those without DCM.

16. The medication with proven anti-inflammatory action (ACE inhibitors, sartans, antialdosteronic drugs, statins and PPRγ receptors activators) could play an important role in the treatment of DCM and AF patients.

Personal contribution

Among original contributions of the thesis we mention:

1. Accomplishment of a development outline (for 1 year) of the patients with AF and dilated cardiomyopathy under treatment with amiodarone.

2. Assessment of sTNF-I role in AF and heart failure pathogeneses.

3. Analysis of the possible role of SRAA genetic polymorphism in the emergence of atrial fibrillation in dilated cardiomyopathy and heart failure patients. Therefore, SRAA inhibition (by use of ACE inhibitors or sartans) may be responsible for prevention of atrial fibrillation emergence in heart failure patients.

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