ORIGINAL ARTICLE

Cardioversion of symptomatic persistent atrial fibrillation in patients with left atrium dilatation: how far should we go?

Cristina Vacarescu[1], Lucian Petrescu[1,2], Cristian Mornos[1,2], Emilia-Violeta Goanta[3], Simina Crisan[1,2], Miruna Ocos[2], Mihai-Andrei Lazar[2], Oana Patru[2], Ramona-Alina Cozlac[2], Dragos Cozma[1,2]

Abstract: Objectives – to assess the outcome of direct current cardioversion (DCCV) in patients (pts) with symptomatic persistent atrial fibrillation (PAF) and LA dilatation. **Methods** – We analyzed 84 pts (49 male) aged 64.6±9.8 y.o, with PAF <1 year, EHRA class >2 and LAVI >40 ml/m^2. Echocardiographic parameters included: ejection fraction (EF), LA diameter (LAD), LA area (LAA) and LA volume (LAV - planimetry 4 chamber view). For each pt we calculated LAVI (left atrium volume index). All pts received proper anticoagulation and antiarrhythmic treatment. The management included a full control of blood pressure before cardioversion during the 3 weeks of prior anticoagulation. Pts with maximum of 3 conversion/year were admitted. **Results** – Arterial hypertension was diagnosed in 80% of pts, while 13% had coronary artery disease. All pts received proper anticoagulation (36 pts on dabigatran, 5 pts on apixaban, 43 pts on acenocumarol with INR values in therapeutic limits) and antiarrhythmic treatment: amiodarone (57 pts), propafenone (4 pts), flecainide (13 pts), sotalol (3 pt), amiodarone+flecainide (7 pts). All 84 pts underwent uncomplicated DCCV (1 to 3 external electrical shocks with energy between 150 and 200 J). Parameters: LAD 4.6±0.6 cm; LAA 30.1±4.8 cm^2 (range 20-46 cm^2); LAV was 114.5±29.5 ml (range 60-220 ml); EF 48.4±7.8 %. Calculated LAVI was 52.37±8.9 ml/m^2. The mean CHA_2DS_2-VASc score was 3.02±1.28. DCCV was successful in restoring sinus rhythm (SR) in 79 pts (94%). The mean total follow-up was 22±9 months, while 25 pts (30%) needed reconversion after 9±4 months. Another 13 pts (15%) were left in permanent AF at the end of the follow-up period. **Conclusion** – Electrocardioversion of symptomatic PAF in LA dilatation showed a positive outcome, even if multiple DCCV and adapted strategy in all pts is needed.
Keywords: atrial fibrillation cardioversion, severe left atrium dilatation, novel oral anticoagulants

Rezumat: Scop – evaluarea siguranței și eficienței electroconversiei fibrilației atriale persistente (PAF) simptomatice la pacienții (pts) cu dilatare de atriu stâng (LA). **Metode –** Am analizat un lot de 84 pts (49 bărbați) cu vârstă medie 64,6±9,8 ani; PAF <1 an, clasă EHRA >2, LAVI >40 ml/m^2. Parametrii ecocardiografici evaluați: fracția de ejecție (EF), diametrul AS (LAD), aria AS (LAA), volumul AS (LAV – planimetrie, apical 4 camere). Pentru fiecare pacient am calculat volumul indexat al AS (LAVI). Managementul pacienților a inclus tratatament antiaritmic, anticoagulant si controlul tensiunii arteriale pe parcursul celor 3 săptamâni de anticoagulare eficientă. Au fost incluși pacienți cu un număr de maxim 3 DCCV/an. **Rezultate –** Hipertensiunea arterială a fost diagnosticată la 80% dintre pacienți; 13% dintre pacienți au prezentat asociat boală coronariană ischemică. Toți pacienții au fost eficient anticoagulați (36 pts – dabigatran, 5 pts – apixaban, 43 pts – acenocumarol, cu menținerea INR în valorile terapeutice) și sub tratament antiaritmic cu: amiodaronă (57 pts), propafenonă (4 pts), flecainidă (13 pts), sotalol (3 pts), amiodaronă + flecainidă (7 pts). S-a tentat electroconversia, fără complicații, pentru toți pacienții evaluați (1 până la 3 șocuri electrice externe, 150-200 J). Parametrii: LAD 4,6±0,6 cm; LAA 30,1±4,8 cm² (între 20-46 cm²); LAV was 114,5±29,5 ml (între 60-220 ml); EF 48,4±7,8 %, LAVI 52.37±8,9 ml/m^2. Scor CHA_2DS_2-VASc mediu: 3,02 ± 1.28. S-a reușit electroconversia la ritm sinusal pentru 79 de pacienți (94%). Perioada medie de urmărire a fost 22±9 luni, timp în care 25 pacienți (30%) au necesitat reinternare pentru DCCV într-un interval de 9±4 luni. La sfârșitul perioadei de urmărire pentru 13 pacienți (15%) s-a considerat fibrilația atrială ca fiind permanentă. **Concluzii –** Acest studiu demonstrează siguranța și eficiența electroconversiei fibrilației atriale persistente simptomatice în prezența dilatării AS, chiar dacă sunt necesare multiple electroconversii și ostrategie antiaritmică adaptată fiecărui pacient.
Cuvinte cheie: electroconversia fibrilației atriale, dilatare severă a atriului stâng, anticoagulanți orali noi

[1] Institute of Cardiovascular Disease, Timisoara, Romania
[2] "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[3] Department of Cardiology, Emergency County Hospital, Craiova, Romania

Contact address:
Cristina Vacarescu, MD, Institute of Cardiovascular Disease, Gh. Adam Street, 13 A, 300310 Timisoara, Romania.
E-mail: vacarescucristina@yahoo.com

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in adults, with a rising incidence in the past decades due to increased life expectancy and improved diagnoses ability. Western European studies report a prevalence ranging from 2.0% to 4.7% of the population[1], and by the end of 2030 it is estimated that in Europe will be 14-17 milion of people with AF[2].

AFFIRM, the largest randomized controlled trial which compared rate versus rhythm control strategies, concluded that is no clear advantage in restoring sinus rhythm[3], nevertheless sustained forms of AF may be associated with increased cardiovascular mortality and remain an aditional target for therapy, particularly in symptomatic patients[1]. At this moment, the 2016 ESC Guidelines for the management of atrial fibrillation recommends a rhythm control therapy to improve symptoms in AF patients who remain symptomatic on adequate rate control therapy, but studies to assess if a modern rhythm control strategy leads to a reduction in major cardiac adverse events (MACE) are still in progress[4].

Assessing factors and predictors of SR maintenance after cardioversion, may be useful for a better identification of patients who would benefit the most from a rhythm control strategy. Atrial remodelling plays an important role in AF reccurence, and lower left atrium index volume (LAVI) represents a strong and independent predictor of SR maintenance after performing a cardioversion[5]. However many other factors such as time in AF, older age, LV function, significant mitral valve disease, rheumatic heart disease are involved in maintaining SR, and a clinical base judgement should be aproach individualised for each patient[6].

Despite a failure to decrease mortality, SR restauration is associated with improvements in symptoms and quality of life, and diminished frequency of AF should be considered an acceptable outcome rather than only accepting as a succes absolute AF supression[7].

PATIENTS AND METHODS

We analyzed a retrospective cohort study of patients hospitalized for atrial fibrillation (PAF) in whom SR was obtain by direct current cardioversion (DCCV). The criteria for patient selection included: hospitalization for PAF (duration <1 year), EHRA class >2, LAVI >40 ml/m^2. Exclusion criteria were defined as: severe valvular disease (severe valvular stenosis and/or regurgitation), more than 3 previous DCCV/year, serum creatinine level >2.5 mg/mL and severe co-morbidity (neoplasia, renal or hepatic failure, severe pulmonary disease, etc).

All patients received proper anticoagulation (direct oral anticoagulants or acenocumarol with INR values in therapeutic range) and antiarrhythmic treatment. In case of unsuccessful DCCV different antiarrhythmic strategies were tried. The management included a full control of blood pressure before cardioversion during the 3 weeks of prior anticoagulation.

Transthoracic echocardiography was performed in all patients before DCCV, and this data was considered the baseline echocardiography. A GE VIVID 7/9 ultrasonographic system (Vivid 7, GE Health Medical, Milwaukee, WI, USA) was used for ultrasound images acquisition, with ECG simultaneously recording for each patient. The echocardiographic examination was performed with patients in the left lateral decubitus position, using standard views and techniques8. Standard echocardiographic measurements included interventricular septum (IVS), left ventricular end-diastolic diameter (LVEDD) and volume (LVEDV), and ejection fraction (LVEF) (Simpson's method). All LA measurements were performed at end-systole just before mitral valve opening and maximal atrium size was considered for evaluation[8]. LA diameter (LAd) was measured by M-mode in the parasternal long-axis view, LA surface area (LAV) and LA volume (LAV) were measured in the apical 4-chamber view.

Data regarding clinical evolution, SR maintenance and major cardiac events (MACE) incidence were obtained by retrospective analyze of patients follow-up visits in the clinic. Participants were followed for 22±9 months from the date of cardioversion. Major cardiac-vascular events were defined as stroke, systemic or pulmonary embolism, myocardial infarction, major bleeding and death.

STATISTICAL ANALYSIS

In Table 1 we present the baseline clinical and demographic features of population as means or percentage (± standard deviation). In Table 3 we analyzed baseline echocardiographic parameters presented as means (± standard deviation) and range. All analyses were performed using OpenEpi (A Collaborative, Open-Source Project in Epidemiologic Computing The OpenEpi Collection of Epidemiologic Calculators, Version 3.01 -- Released April 4 and revised April 6, 2013). Continuous variables were compared between groups using unpaired *t* test (variables with normal distribution) or Mann-Whitney U test (non-normally distributed variables). A p value <0.05 was considered significant.

RESULTS

This study included 84 patients (49 male, aged 64.6±9.8 y.o). The demographic and clinical characteristics are presented in Table 1, antiarrhythmic and anticoagulant treatment are presented in Table 2.

Uncomplicated direct current cardioversion, using 1 to 3 external electrical shocks with energy between 150 and 200 J, was performed in all patients. In case of unsuccessful DCCV, different antiarrhythmic strategies were tried and another attempt of cardioversion was made during the same hospitalization. In the amiodarone group 9 patients failed to convert to SR after first attempt of DCCV: for 3 of them we added flecainide, 2 were switched from amiodarone to sotalol and 4 pts were switched from amiodarone to flecainide.

DCCV was successful in restoring sinus rhythm in 79 pts (94 %), for 5 pts AF was considered permanent. The mean total follow-up was 22±9 months, while 25 pts (30%) needed reconversion after 9±4 months. Another 13 pts (15%) were left in permanent AF at the end of the follow-up period. There were no major cardiac events, no embolic events, major bleeding events, or deaths during the follow up period.

The main echocardiographic parameters of all patiens at baseline are presented in Table 3, togheter with the echocardiographic characteristics for the 2 groups: SR group and permanent AF group at the end of the follow up period.

All pts had moderate to severe LA dilatation with LAVI >40 ml/m^2, (LAVI mean±SD: 52.37 ± 8.9 ml/m^2, LAVI range 87.18-40.21 ml/m^2). LA area and volume, LA volume index and EF were echocardiographical parameters with statistical significance ($p<0.05$). In the permanent AF group we found a higher incidence of hypertension, coronary artery disease and dilated cardiomyopathy. We obtain no significant statistical difference between the SR group and the permanent AF group regarding age or sex distribution.

DISCUSSION

In the present patient cohort with moderate to severe LA dilatation and symptomatic persistent AF, electrical cardioversion was safe and feasable with a good outcome for a high number of pts. LAVI represents a strong predictor of SR maintanance after DCCV, and we also find a significant statistical difference between the 2 groups: SR pts and permanent AF pts, but note that both groups of pts had severe LA dilatation, with LAVI >40 ml/m^2. Recent studies suggest that novel ecocardiographic parameters such as atrial emptying fraction, right atrial volume or different index combinig diastolic and sistolic Tissue Doppler parameters can be use to predict AF recurrence after DCCV[9,10,11]. With all this, the best ecocardiographical and clinical predictor of SR maintanance is yet to be validated.

Due to the retrospective study design, one of the major limitations was the inability of assessing reliable data regarding more complex ecochardiographic parameters such as diastolic function, strain parameters.

Clinical score as HATCH (where the acronym stands for hypertension, age >75 years, transient ischaemic attack or stroke, chronic obstructive pulmonary disease, and heart failure) is useful in predicting short-term success of DCCV at early stages for patients with AF, for whom the use of a rhythm-control strategy is planned[12], but literature data is sparse regarding DCCV in pts with persistent AF and severe LA dilatation.

An adapted antiarrhythmic treatment strategy can play a key role in achieving SR or SR maintenance after DCCV, as is also suggested by a recent data-mining project of the Flecainide Short-Long trial which states

Table 1. Baseline features of study population

	All Patients (N = 84)
Mean age, years (SD)	64.6 (9.8)
Mean follow-up, months (SD)	22 (9)
Male, n (%)	49 (58)
Hypertension, n (%)	67 (80)
Diabetes mellitus, n (%)	16 (19)
CHA_2DS_2-VASc score, (SD)	3.02 (1.28)
Coronary artery disease, n (%)*	11 (13)
Dilated cardiomyopathy, n (%)	9 (11)
Chronic kidney disease, n (%)**	30 (36)

* Coronary artery disease = documented angina/myocardial infarction.
** Chronic kidney disease defined as reduction in creatinine clearance <90 ml/min. None of the patients in our cohort had creatinine clearance <30 ml/min.

Table 2. Antiarrhythmic and anticoagulant treatment

Antiarrhythmic treatment	All patients (N=84)
Amiodarone, n (%)	57 (67.8)
Propafenone, n (%)	4 (4.7)
Flecainide, n (%)	13 (15.4)
Sotalol, n (%)	3 (3.5)
Amiodarone + flecainde, n (%)	7 (8.3)
Anticoagulant treatment	**All patients (N = 84)**
Dabigatran, n (%)	36 (42.8)
Apixaban, n (%)	5 (5.9)
Acenocumarol, n (%)*	(51.1)

*with INR values in therapeutic limits

Table 3. Main echocardiographic parameters

	All patients (baseline) (N=84)		SR group (end of the study) (n=66)	Permanent AF group (end of the study) (n=18)	P*
Echocardiographic parameters	**Mean ± SD**	**Range**	**Mean ± SD**	**Mean ± SD**	
IVS (mm)	12.9±1.9	11-23	12.9±2	12.7±1.4	0.629
EF (%)	48.4±7.8	20-60	49.6±6.6	45±7.2	0.021
LVEDV (ml)	120±47.8	70-330	115±41	126.7±41.8	0.299
LAd (cm)	4.6±0.6	3.3–6.7	4.6±6.6	4.8±0.4	0.807
LAA (cm^2)	30.1±4.8	20-46	29.8±4.7	32.3±2.7	0.005
LAV (ml)	114.9±29.5	60-220	112.3±28.9	127.9±16.6	0.004
LAVI (ml/m^2)	52.37±8.9	87.18-40.21	46.7±4.3	53.4±9.2	0.007

*P values for comparisons between SR and permanent AF groups

that a strategy of flecainide pretreatment for 48 h prior to planned electrical cardioversion may be a useful planning of a strategy of long-term rhythm control[13].

Earlier studies showed that a rhythm control strategy has no clear advantges on long term mortality compared to a rate control approach, but the situation is changing in the last years due to tehnical advance in interventional therapy for this arrhythmia and also the progression in better defining and diagnosing the high risks associated with AF, such as asymptomatic brain embolisations and AF-related brain hypoperfusion[14]. CABANA and EAST-AFNET[4] are two undergoind, randomized, open label trials which asses the benefits of an interventional rhythm control strategy in preventing complication of AF[15,16]. A recent study published in January 2017 which included 6.545 participants with AF without heart failure (HF) at baseline, analysed the significant clinical predictors of incident HF and its prognostic effect on long-term outcomes and concluded that HF among patients with AF is common, is more likely to be HF with preserved ejection fraction, and is associated with poor long-term outcomes[17], so the question if is there a need to treat AF aggressively still remains a subject of debate.

CONCLUSION

Electrocardioversion of symptomatic persistent atrial fibrillation in severe left atrium dilatation showed a positive outcome, even if multiple electrocardioversion and adapted strategy in all patients is needed.

Conflict of interest: None declared.
Authors' contributions: Concept/design: Cristina Vacarescu (CV), Lucian Petrescu (LP), Cristian Mornos (CM), Emilia-Violeta Goanta (EMG), Simina Crisan (SC), Miruna Ocos (MO), Mihai-Andrei Lazar (MAL), Oana Patru (OP), Ramona-Alina Cozlac (RAC), Dragos Cozma (DC). Critical revision of article: Dragos Cozma (DC), Lucian Petrescu (LP), Cristian Mornos (CM), Simina Crisan (SC).

Abbreviations

DCCV – Direct Current Cardioversion
EF – Ejection Fraction
HR – Heart Failure
INR – International Normalized Ratio
IVS – Interventricular Septum
LA – Left Atrium
LAA – Left Atrial Area

Table 4. Comparison of demographic data between SR group and permanent AF group

	SR group (N=66)	Permanent AF group (N=18)	P*
Mean age, years (SD)	65.4±9	62.4±12	0.2481
Hypertension, n (%)	56 (85)	11 (61)	0.0253
Male	38 (58)	11 (61)	0.8199
Diabetes mellitus, n (%)	10 (15)	6 (33)	0.0854
Coronary artery disease, n (%)	5 (8)	6 (33)	0.0060
Dilated cardiomyopathy, n (%)	2 (3)	7 (39)	<0.0001
Chronic kidney disease, n (%)	21 (32)	9 (50)	0.1606

*P values for comparisons between SR and permanent AF groups

Lad – Left Atrium Diameter
LAV – Left Atrial Volume
LAVI – Left Atrial Volume Index
LV – Left Ventricule
LVEDD – Left Ventricular End-Diastolic Diameter
LVEDV – Left Ventricular End-Diastolic Volume
MACE – Major Cardiac Events
PAF – Persistent Atrial Fibrillation
RA – right atrium
SR – Sinus Rhythm

References

1. Shukla A, Curtis AB. Avoiding permanent atrial fibrillation: treatment approaches to prevent disease progression. Vasc Health Risk Manag. 2014;10:1-12. doi: 10.2147/VHRM.S49334
2. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014 Jun 16;6:213-20. doi: 10.2147/CLEP.S47385
3. Corley SD, Epstein AE, DiMarco JP, et al; AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation. 2004; 109(12):1509-1513.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016 Nov;18(11):1609-1678. Epub 2016 Aug 27
5. Akdemir B, Altekin RE, Küçük M, Yanikoglu A, Karakaş MS, Aktaş A, Demir I, Ermiş C. The significance of the left atrial volume index in cardioversion success and its relationship with recurrence in patients with non-valvular atrial fibrillation subjected to electrical cardioversion: a study on diagnostic accuracy. Anadolu Kardiyol Derg. 2013 Feb;13(1):18-25. doi: 10.5152/akd.2013.003
6. Abu-El-Haija B, Giudici MC. Predictors of long-term maintenance of normal sinus rhythm after successful electrical cardioversion. Clin Cardiol. 2014 Jun;37(6):381-5. doi: 10.1002/clc.22276. Epub 2014 Apr 3.
7. Morin DP, Bernard ML, Madias C, Rogers PA, Thihalolipavan S, Estes NA 3rd. The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment. Mayo Clin Proc. 2016 Nov 5. pii: S0025-6196(16)30538-9. doi: 10.1016/j.mayocp.2016.08.022
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the american society of echocardiography and the European association of cardiovascular imaging. Eur Heart J Cardiovasc Imaging 2015; 16:233-71.
9. Luong CL, Thompson DJ, Gin KG, Jue J, Nair P, Lee PK, Tsang MY, Barnes ME, Colley P, Tsang TS. Usefulness of the Atrial Emptying Fraction to Predict Maintenance of Sinus Rhythm After Direct Current Cardioversion for Atrial Fibrillation. Am J Cardiol. 2016 Nov 1;118(9):1345-1349. doi: 10.1016/j.amjcard.2016.07.066. Epub 2016 Aug 13
10. Luong C, Thompson DJ, Bennett M, Gin K, Jue J, Barnes ME, Colley P, Tsang TS. Right atrial volume is superior to left atrial volume for prediction of atrial fibrillation recurrence after direct current cardioversion. Can J Cardiol. 2015 Jan;31(1):29-35. doi: 10.1016/j.cjca.2014.10.009. Epub 2014 Oct 12.
11. Ari H, Ari S, Sarigül OY, Coşar S, Doganay K, Emlek N, Tütüncü A, Kivanç E, Çamci S, Aktaş I, Karakuş A, Zengin I, Bozat T, Melek M. A Novel Index Combining Diastolic and Systolic Tissue Doppler Parameters for Prediction of Atrial Fibrillation Recurrence. Echocardiography. 2016 Jul;33(7):1009-15. doi: 10.1111/echo.13212. Epub 2016 Mar 20.
12. Emren SV, Kocabaş U, Duygu H, Levent F, Şimşek EÇ, Yapan Emren Z, Tülüce S - The role of HATCH score in predicting the success rate of sinus rhythm following electrical cardioversion of atrial fibrillation. Kardiol Pol. 2016;74(9):978-84. doi: 10.5603/KP.a2016.0044. Epub 2016 Apr 4.
13. Oto E, Okutucu S, Katircioglu-Öztürk D, Güvenir HA, Karaagaoglu E, Borggrefe M, Breithardt G, Goette A, Ravens U, Steinbeck G, Wegscheider K, Oto A, Kirchhof P. Predictors of sinus rhythm after electrical cardioversion of atrial fibrillation: results from a data mining project on the Flec-SL trial data set. Europace. 2016 Jul 4. pii: euw144.
14. Kautzner J. [Is there a need to treat atrial fibrillation aggressively?]. Vnitr Lek. 2015 May;61(5):417-20.
15. ClinicalTrials.gov. Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA). https://clinicaltrials.gov/ct2/show/NCT00911508
16. ClinicalTrials.gov. Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST). http://www.easttrial.org
17. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, Kowey PR, Mahaffey KW, Hylek E, Peterson ED, Piccini JP, Fonarow GC; ORBIT-AF Investigators and Patients. Predictors and Prognostic Implications of Incident Heart Failure in Patients With Prevalent Atrial Fibrillation, JACC Heart Fail. 2017 Jan;5(1):44-52. doi: 10.1016/j.jchf.2016.09.016.