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Original Research

The Impact of Right Atrial Size to Predict Success of Direct Current Cardioversion in Patients With Persistent Atrial Fibrillation

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AUTHOR'S SUMMARY

Atrial fibrillation (AF) is a disease of the left atrium. However, immediate success of direct current cardioversion (DCCV) in AF patients is associated with AF duration, sex, presence of cardiovascular diseases, and medication intake, whereas left atrial (LA) size has weak or no prognostic value. Recent studies revealed that right atrial (RA) size rather than LA size has a higher predictivity for early/intermediate AF recurrence after DCCV or after AF ablation. We demonstrate that the simple echocardiographic measurement of the RA area but not the LA volume could help determine the immediate success of DCCV in patients with AF.

ABSTRACT

Background and Objectives: The prognostic implication of right atrial (RA) and left atrial (LA) size for an immediate success of direct current cardioversion (DCCV) in atrial fibrillation (AF) remains unclear. This study aimed to compare RA and LA size for the prediction of DCCV success.
Methods: Between 2012 and 2018, 734 consecutive outpatients were screened for our prospective registry. Each eligible patient received a medical history, blood analysis, and transthoracic echocardiography with a focus on indexed RA (iRA) area and LA volume (iLAV) prior to DCCV with up to three biphasic shocks (200-300-360 J) or additional administration of amiodarone or flecainide to restore sinus rhythm.
Results: We enrolled 589 patients, and DCCV was in 89% (n=523) successful. Mean age was 68 ± 10 years, and 40% (n=234) had New York heart association class >II. A prevalence of the male sex (64%, n=376) and of persistent AF (86%, n=505) was observed. Although DCCV success was associated with female sex (odds ratio [OR], 1.88; 95% confidence interval [CI], 1.06–3.65), with absence of coronary heart disease and normal left ventricular function (OR, 2.24; 95% CI, 1.26–4.25), with short AF duration (OR, 1.93; 95% CI, 1.05–4.04) in univariable regression, only iRA area remained a stable and independent predictor of DCCV success (OR, 0.27; 95% CI, 0.12–0.69; area under the curve 0.71), but not iLAV size (OR, 1.16; 95% CI, 1.05–1.56) in multivariable analysis.
Conclusions: iRA area is superior to iLAV for the prediction of immediate DCCV success in AF.

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Author Contributions
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Keywords: Atrial fibrillation; Electrical cardioversion; Transthoracic echocardiography; Right atrium

INTRODUCTION

Atrial fibrillation (AF) is the most common type of cardiac arrhythmias. It has a high prevalence in the general population and is responsible for significant morbidity, mortality, and health care expenditures in affected individuals. Restoring sinus rhythm may not only relief symptoms but may also prevent further adverse clinical outcomes.[1] With this regard direct current cardioversion (DCCV) is an easily accessible and feasible method for converting AF to sinus rhythm with high success rates.[2] Several clinical parameters, such as age, sex, duration of AF, cardio-vascular risk factors and comorbidities have been identified as predictors of the immediate post-DCCV outcome.[3-5] However, there are inconclusive data on the relationship between distinct echocardiographic parameters and DCCV success.[6-8] AF is considered to be a manifestation of left atrial (LA) disease, and the relationship between atrial remodeling and AF has been extensively investigated.[9] However, using solely LA size to identify patients who will immediately benefit from DCCV remains inconclusive in daily practice.[3][6][7] In the recent years, right atrial (RA) remodeling has attracted considerable clinical attention in AF. While both the RA and LA undergo remodeling, studies have shown that RA remodeling follows a different pattern and is independently associated with worse clinical outcomes in AF patients, particularly with increasing AF duration.[10][11] RA enlargement decreases after sinus rhythm restoration, and, compared to LA size, RA dimensions seem to be more closely related to early and mid-term AF recurrence after radio-frequency ablation or DCCV.[12-14]

However, the role of the RA for the immediate outcome of DCCV is still not fully understood. We hypothesized that the size of the RA may be more relevant for the DCCV success than the dimensions of the LA. We aimed to investigate the clinical and echocardiographic predictors of DCCV outcome with particular focus on the relevance of RA and LA size in a large cohort of patients presenting with AF. In addition, we studied the relevance of RA size with AF type.

METHODS

Ethical statement

The protocol of this study was approved by the Institutional Review Board of the Technische Universität Dresden, Germany (#345092011) and written informed consent form was waived due to the observational nature of this study. All patients were treated in accordance with the ethical guidelines of the 2013 Declaration of Helsinki and according to our institutional routine clinical protocol. Written consent acknowledging the risks associated with all standard treatment modalities (i.e., oral anticoagulation, transesophageal echocardiography, sedation, and DCCV) was obtained from all patients.

Study design

A total of 734 outpatients were referred for an elective DCCV procedure due to symptoms for AF between 2012 and 2018 to our center. Patients had either persistent AF or long-standing persistent AF according to the standardized definition.[1] Main exclusion criteria were paroxysmal AF, prior DCCV or pharmacological CV, ablation for AF within the

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previous 3 months or hemodynamic instability of the patient. Only eligible patients were consecutively enrolled in this observational registry at the Herzzentrum, Dresden, Germany. At the day of DCCV a detailed medical history of each patient was obtained together with a 12-lead electrocardiography to confirm AF, blood analysis, and standardized transthoracic echocardiography (TTE).

Transthoracic echocardiography

TTE measurements of left and right ventricular dimensions and systolic and diastolic function, as well as quantification of valvular diseases, were performed prior to CV according to the existing guidelines and averaged from 3 cardiac cycles.[15] A detailed description is provided in the supplementary data section. In brief, LA volume was measured at end-systole using the biplane Simpson method from dedicated images of the left atrium acquired in both the apical 4-chamber and 2-chamber views (averaged from 3 cardiac cycles). RA area was assessed at ventricular end-systole by measuring in the right ventricle-focused apical 4-chamber view averaged from 3 cardiac cycles. Care was taken to represent the largest appearance of the RA and wall contouring was performed from the lateral tricuspid annulus via the atrial roof to the septal tricuspid annulus at the insertion of the interatrial and interventricular septum. An example is provided in the supplementary data section (**Supplementary Figure 1**). LA volume and RA area were indexed to body-surface-area (iLAV and iRA area). Normal left ventricular ejection fraction (LVEF) was regarded as >50%, elevated right ventricular systolic pressure (RVSP) >35 mmHg, reduced tricuspid annular plane systolic excursion (TAPSE) <16 mm, dilated iLAV ≥37 mL/m^2 and enlarged iRA area ≥10.5 cm^2/m^2.[16] As RA areas were measured only by an experienced examiner who was blinded to clinical status and outcome, second measurements on 50 randomly selected clips were performed independently by another blinded examiner to assess inter-observer reliability.

Direct current cardioversion procedure and definition of cardioversion success

DCCV was performed in the intensive care unit with continuous monitoring of heart rate, rhythm, blood pressure, breathing rate, and oxygen saturation. Patients were sedated with intravenous propofol or etomidate and were monitored for 2 hours after the procedure. DCCV was performed exclusively with patches in the anterior-posterior position, when necessary the pressure on the pads was increased. The DCCV procedure consisted of a QRS-synchronized biphasic direct current shock (biphasic, Medtronic LIFEPACKVR 20, Redmond, WA, USA) starting with 200 J and increasing serially to 300 J and then to 360 J until sinus rhythm was achieved. If sinus rhythm was not achieved after 360 J or immediate recurrence of AF (IRAF) occurred, we administered intravenous amiodarone or flecainide (5 mg/kg, < 300 mg or 1.5 mg/kg, <150 mg). To our knowledge, the defibrillators used in our study are the only devices capable of delivering biphasic 360 J, and at the time of study enrollment (since 2012), we followed in the absence of clear guideline recommendations the DCCV protocol of a collaborative study group.[3] For further analysis, patients with an unsuccessful DCCV were stratified as follows: i) true failure without even a single beat of sinus rhythm after DCCV; or ii) IRAF within first minutes after DCCV. Anticoagulation was strictly maintained within the therapeutic range after DCCV. After 4 weeks, continuation of oral anticoagulation was re-assessed depending on the CHA2DS2-VASc (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female) score and the presence of AF.

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Data handling and categorization of variables

The patients' medication and routine blood analyses, main diagnosis, and comorbidities were assessed at the time of admission. A history of coronary artery disease (CAD) was defined as presence of previous myocardial infarction, myocardial revascularization, or significant coronary artery stenosis on angiography. Coronary heart disease (CHD) was defined as the presence of CAD with reduced LVEF. Valvular heart disease was defined as presence of at least moderate stenosis or moderate regurgitation of a cardiac valve. Cardiovascular risk factors were defined as the presence of a combination of at least two of the following conditions: arterial hypertension, dyslipidemia, diabetes mellitus, or obesity. Pulmonary disease was defined as the presence of chronic obstructive pulmonary disease, elevated RVSP >35 mmHg, or other diseases affecting the lungs. White blood cell count, red blood cell count, hemoglobin, creatinine, C-reactive protein, and thyroid-stimulating hormone were classified as pathological or normal according to the gender-specific nomograms of our in-house laboratory. Further detailed information can be found in the supplementary data section.

Statistical analysis

Categorical data are presented as counts (percentages), and continuous variables are presented as means with standard deviations or medians with interquartile ranges (first quartile and third quartile). The χ^2 test or Fisher's exact test was used for comparisons of categorical variables as appropriate. The unpaired t-test or Wilcoxon test was used to compare continuous variables as appropriate, and Bonferroni adjustment was performed for multiple testing. The Kendall rank correlation coefficient tau was used to measure the association between two continuous variables. Binary logistic models were used to model the conditional probabilities of a successful DCCV with adjustments as indicated. Hereby, continuous variables were fitted using restricted cubic splines with four knots located at the 5th, 35th, 65th and 95th percentiles so as to not assume linear relationships between them and the outcome variables.[17] Additionally, odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were calculated. Hereby, ORs were presented as interquartile range effects (first quartile: third quartile) to describe relative chances of a successful DCCV (**Table 1**). We relaxed the "rule of the thumb" with 6 events-per-variable to determine the maximum number of covariates to use in the multivariable regression models.[18] The parameters were chosen both a priori based on clinical relevance (see Introduction) and on statistically significant difference in the univariable regression analysis ($p<0.05$). Interaction analyses were performed between the main echocardiographic parameters RA and LA size and with each of the co-variable, that was identified as clinically or statistically significant for DCCV outcome in the previous multivariable analysis. Internal validation of regression models was conducted using the bootstrapping method (2000 repetitions), and the optimism-corrected area under the curve (AUC) with the corresponding 95% CI was obtained. All regression estimates and probabilities presented were derived from the bootstrap covariance and distribution technique (5000 replicates). The inter-observer reliability of the RA area was assessed on 50 randomly selected clips using the coefficient of variation (CV) and the intraclass correlation coefficient (ICC) with correlation and Bland-Altman plot for visualization.[19] The final statistical significance was a two-tailed p value <0.05. All analyses were performed using the statistical programming language R (V.3.0.2, 2013; The R Foundation for Statistical Computing, Vienna, Austria) and the R "rms" package.[20]

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Table 1. Univariable and multivariable logistic regression analyses regarding a successful direct current cardioversion

Parameters	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (years, from 62 to 75)	2.62 (1.24–4.91)	0.044	1.21 (0.81–1.82)	0.349
Female vs. male sex	1.88 (1.06–3.65)	0.042	1.87 (0.84–3.56)	0.109
Body mass index (kg/m^2, from 25 to 30)	0.96 (0.71–1.21)	0.556		
Baseline AA medication (no vs. yes)	1.95 (1.07–4.04)	0.045	1.81 (0.79–3.50)	0.094
CHA2DS2-VASc (score, from 2 to 4)	1.13 (0.82–1.56)	0.425		
Prev. episode of stroke or TIA (no vs. yes)	1.78 (0.75–8.53)	0.625		
Hyperthyroidism (no vs. yes)	2.29 (0.85–10.38)	0.485		
Cardiovascular risk factors (no vs. yes)	1.51 (0.86–2.51)	0.120		
Coronary artery diseases (no vs. yes)	2.24 (1.26–4.25)	0.010	1.61 (0.66–4.08)	0.295
Pulmonary disease (no vs. yes)	1.15 (0.62–2.81)	0.697		
LV ejection fraction (%, from 45 to 60)	1.46 (0.74–2.59)	0.095	1.31 (0.64–2.54)	0.651
RV dysfunction (no vs. yes)	1.71 (0.85–4.34)	0.181		
E/Em - ratio (from 8 to 11)	0.97 (0.72–1.18)	0.521		
LA volume index (mL/m^2, from 29 to 41)	1.16 (0.75–1.56)	0.901	1.26 (0.87–1.91)	0.497
RA area index (cm^2/m^2, from 8 to 11)	0.26 (0.13–0.59)	<0.001	0.27 (0.12–0.69)	<0.001
Moderate or severe valve disease (no vs. yes)	2.78 (1.35–6.68)	0.012	1.59 (0.56–4.28)	0.415
Persistent vs. long persistent AF	1.93 (1.05–4.04)	0.041	1.54 (0.73–3.53)	0.267

OR are presented with 95% CI with lower and upper bound. In the Parameters column, unit and first to third interquartile range are given in parentheses for continuos variables, e.g. age (years, from 62 to 75). Of note, an increase in iRA would decrease the OR and therefore the probability of a successful direct current cardioversion. Regressions and results are based on 5000 bootstrap repetitions.
AA = antiarrhythmic; AF = atrial fibrillation; CHA2DS2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or TIA, vascular disease, age 65 to 74 years, female; CI = confidence interval; LA = left atrial; LV = left ventricular; OR = odds ratio; pulmonary disease = presence of chronic obstructive pulmonary disease, elevated RVSP >35 mmHg, or other diseases affecting the lungs; RA = right atrial; RV dysfunction = presence of a reduced tricuspid annular plane systolic excursion <16 mm; TIA = transient ischemic attack.

RESULTS

Clinical and echocardiographic baseline characteristics of patients

The final study population consisted of 589 patients, and the main clinical and echocardiographic baseline characteristics are presented in **Tables 2** and **3**. In brief, male sex was predominant, cardiovascular risk factors were common, and the majority of patients (86%) had persistent AF at admission. iLAV and iRA area were enlarged in 34% (n=202) and 28% (n=164) of patients, respectively, but only iRA area had a correlation with AF type (**Figure 1A and B**). There were no statistically significant differences between male and female patients for atrial sizes (iRA area: 9.8±2.5 vs. 9.8±2.6 cm^2/m^2, p=0.708; iLAV: 36.4±12.1 vs. 37.2±11.4 mL/m^2, p=0.201).

Direct current cardioversion procedure

DCCV was successful in 523 patients (89%). In accordance with the protocol, patients with unsuccessful DCCV received more shocks, higher median cumulative shock energy and necessitated more often adjunctive antiarrhythmic medication than patients with a successful DCCV (3.0 vs. 1.2, p<0.001; 860 J vs. 250 J, p<0.001; 100% (n=66) vs 4% (n=21), p<0.001, respectively). The adjunctive medication consisted of 80% amiodarone (n=70) and 20% flecainide (n=17). Of note, iRA area correlated with the number of DCCV tries and cumulative shock energy levels respectively, but not iLAV (iRA area 8.9±2.3 vs. 11.2±2.8 cm^2/m^2, p<0.001; iLAV: 35.8±11.9 vs. 37.2±11.7 mL/m^2, p=0.432).

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Table 2. Baseline demographic and clinical characteristics

Variables	Overall (n=589)	Successful DCCV (n=523)	Unsuccessful DCCV (n=66)	p value
Age (years)	68±10	68±10	67±10	0.204
Female sex	213 (36)	197 (38)	16 (24)	0.032
Body mass index (kg/m^2)	28.2±4.5	28.1±4.6	28.3±4.1	0.438
NYHA classes II–IV	234 (40)	204 (39)	30 (45)	0.313
Creatinine clearance (mL/min)	77±20	77±20	76±19	0.291
CHA2DS2-VASc score	3.2±1.6	3.2±1.6	3.0±1.6	0.412
Antiarrhythmic medication (Class I, III)	77 (13)	63 (12)	14 (21)	0.037
Digitoxin medication	65 (11)	55 (11)	10 (15)	0.235
Betablocker medication	522 (89)	465 (89)	57 (86)	0.539
Systemic inflammation	21 (4)	18 (3)	3 (5)	0.649
Hyperthyroidism	23 (4)	18 (3)	5 (8)	0.115
Anaemia	106 (18)	95 (18)	11 (17)	0.765
Arterial hypertension	470 (79)	420 (80)	50 (76)	0.386
Diabetes mellitus	157 (27)	141 (27)	16 (24)	0.638
Dyslipidemia	263 (45)	240 (46)	23 (35)	0.109
Coronary heart disease	93 (16)	75 (14)	18 (27)	0.007
Chronic obstructive lung disease	28 (5)	26 (5)	2 (3)	0.458
Previous episode of stroke/TIA	30 (5)	25 (4)	5 (8)	0.253
Type of atrial fibrillation				0.037
Persistent	505 (86)	454 (87)	51 (77)	
Long persistent	84 (14)	69 (13)	15 (23)	

Data are presented as mean ± standard deviation and absolute numbers with relative frequencies (%).
CHA2DS2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or TIA, vascular disease, age 65 to 74 years, female; DCCV = direct current cardioversion; NYHA = New York Heart Association; TIA = transient ischemic attack.
p-value denotes significance levels of unpaired t-test or Wilcoxon-test, χ^2-test or Fisher's exact test as appropriate.

Table 3. Echocardiographic baseline characteristics

Variables	Overall (n=589)	Successful DCCV (n=523)	Unsuccessful DCCV (n=66)	p value
LV ejection fraction (%)	51.5±10.2	51.8±9.9	48.7±11.5	0.034
LV end-diastolic diameter (mm)	48.3±6.9	48.3±6.7	48.8±8.1	0.638
LV end-systolic diameter (mm)	34.3±7.6	34.2±7.5	35.4±8.5	0.460
LV end-diastolic septal wall (mm)	12.4±1.9	12.4±1.9	12.6±1.6	0.066
LA diameter (mm)	43.7±4.7	43.6±4.6	44.2±5.6	0.098
LA volume (mL)	69.9±23.0	69.2±22.9	74.1±25.1	0.216
LA volume index (mL/m^2)	35.8±11.9	35.6±11.9	37.3±11.7	0.310
E/Em - ratio	9.8±3.5	9.8±3.5	10.0±3.8	0.586
RV systolic pressure (mmHg)	34.0±10.8	33.8±10.5	35.6±13.3	0.424
TAPSE (mm)	20.9±4.1	21.0±4.0	20.3±4.4	0.027
RA area (cm^2)	18.8±5.1	18.4±4.7	22.5±7.1	<0.001
RA area index (cm^2/m^2)	9.6±2.6	9.4±2.3	11.4±3.8	<0.001
Valvular disease >moderate	51 (8)	41 (8)	10 (17)	0.016
Aortic valve stenosis	8 (1)	6 (1)	2 (3)	
Aortic valve regurgitation	19 (3)	17 (3)	2 (3)	
Mitral valve stenosis	1 (0)	0 (0)	1 (0)	
Mitral valve regurgitation	10 (2)	8 (2)	2 (3)	
Tricuspid valve regurgitation	12 (2)	10 (2)	2 (3)	

Data are presented as mean ± standard deviation and absolute numbers with relative frequencies (%).
DCCV = direct current cardioversion; E/Em = peak early diastolic filling (E) and early diastolic lateral mitral annular velocity (Em); LA = left atrial; LV = left ventricular; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.
p denotes the significance levels of unpaired t-test or Wilcoxon-test, χ^2-test or Fisher's exact test as appropriate.

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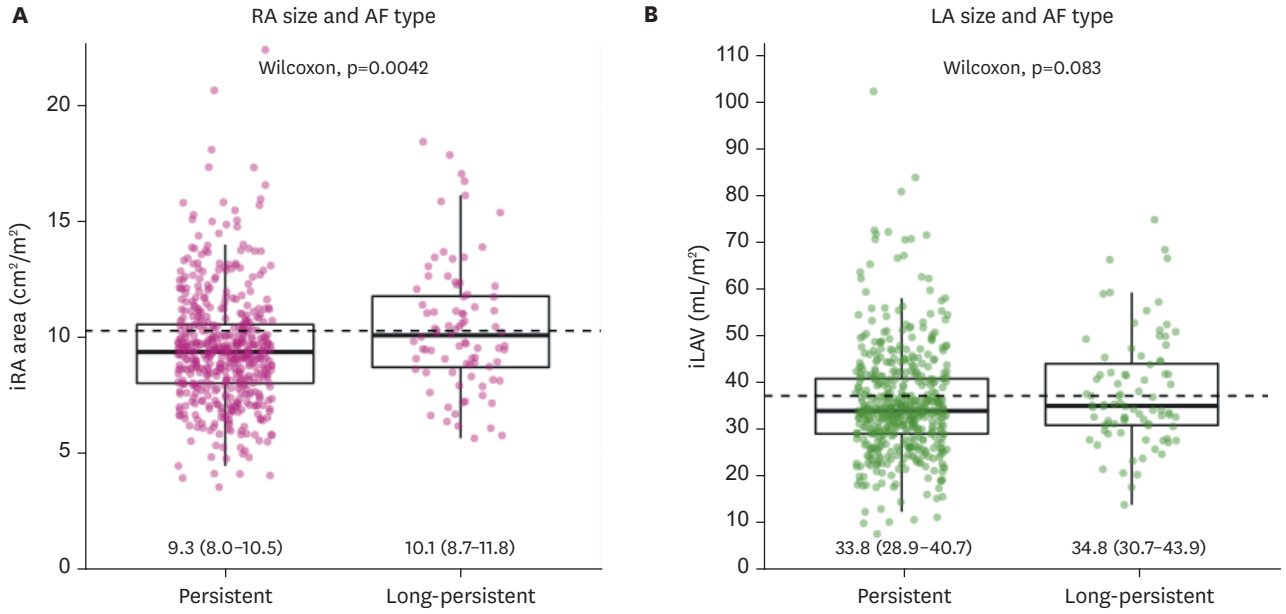

Figure 1. Comparison of both iRA area (A) and iLAV (B) with AF type. The dashed horizontal lines represent the cut-off values for iRA area >10.5 cm²/m² and iLAV >37 mL/m².
AF = atrial fibrillation; DCCV = direct current cardioversion; iLAV = indexed left atrial volume; iRA = indexed right atrial; LA = left atrial; RA = right atrial.

Clinical and echocardiographic predictors of direct current cardioversion success

Differences in baseline characteristics and echocardiographic parameters between patients with and without successful DCCV are described in **Tables 2** and **3**. Patients with successful DCCV were more often female, had higher incidence of persistent AF, less frequent CHD, and received less often antiarrhythmic drugs at baseline. In addition, they had higher LVEF, higher TAPSE, smaller iRA area, and were less likely to have more than moderate valve disease than patients with unsuccessful DCCV. Neither the prevalence of tricuspid regurgitation, chronic obstructive pulmonary disease, nor right ventricular peacemaker leads differed between patient groups. The DCCV success was significantly influenced by iRA area (AUC, 0.69; 95% CI, 0.62–0.76; p<0.001) but not by iLAV size (AUC, 0.52; 95% CI, 0.45–0.59; p=0.532) as shown in **Figure 2**. Although sex, antiarrhythmic medication at baseline, CHD, valve disease, LVEF, and AF type were significant predictors of DCCV outcome in univariable analysis (**Table 1**, **Figure 3**), only iRA area remained an independent predictor in the multivariable regression model (AUC, 0.71; 95% CI, 0.65–0.77; p<0.001), as shown in **Table 1**. Although iRA area and iLAV were positively correlated (tau=0.28, p<0.001), we found no significant interaction between iRA area and iLAV with DCCV outcome in the analyses (p=0.813). As summarized in **Table 4**, the effect of iRA area on DCCV success was consistent in the interaction analysis for the main covariates.

Inter-observer reliability

The CV and ICC for RA area between two independent investigators were 4.6% and 0.98 (p<0.001). The corresponding correlation plot and Bland-Altman plot are shown in the supplementary data section (**Supplementary Figure 2**).

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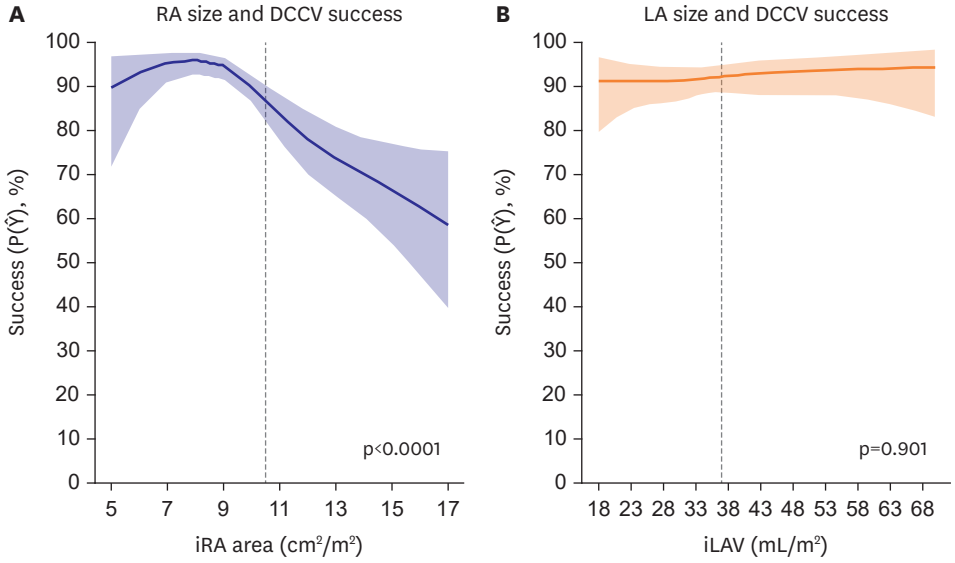

Figure 2. Overall probability (P) of DCCV success as a function of RA (A) and LA size (B) derived from the full regression model in **Table 1** with the 95% confidence interval (gray area). The dashed horizontal lines represent the cut-off values for iRA >10.5 cm^2/m^2 and iLAV >37 mL/m^2.
AF = atrial fibrillation; DCCV = direct current cardioversion; iLAV = indexed left atrial volume; iRA = indexed right atrial; LA = left atrial; RA = right atrial.

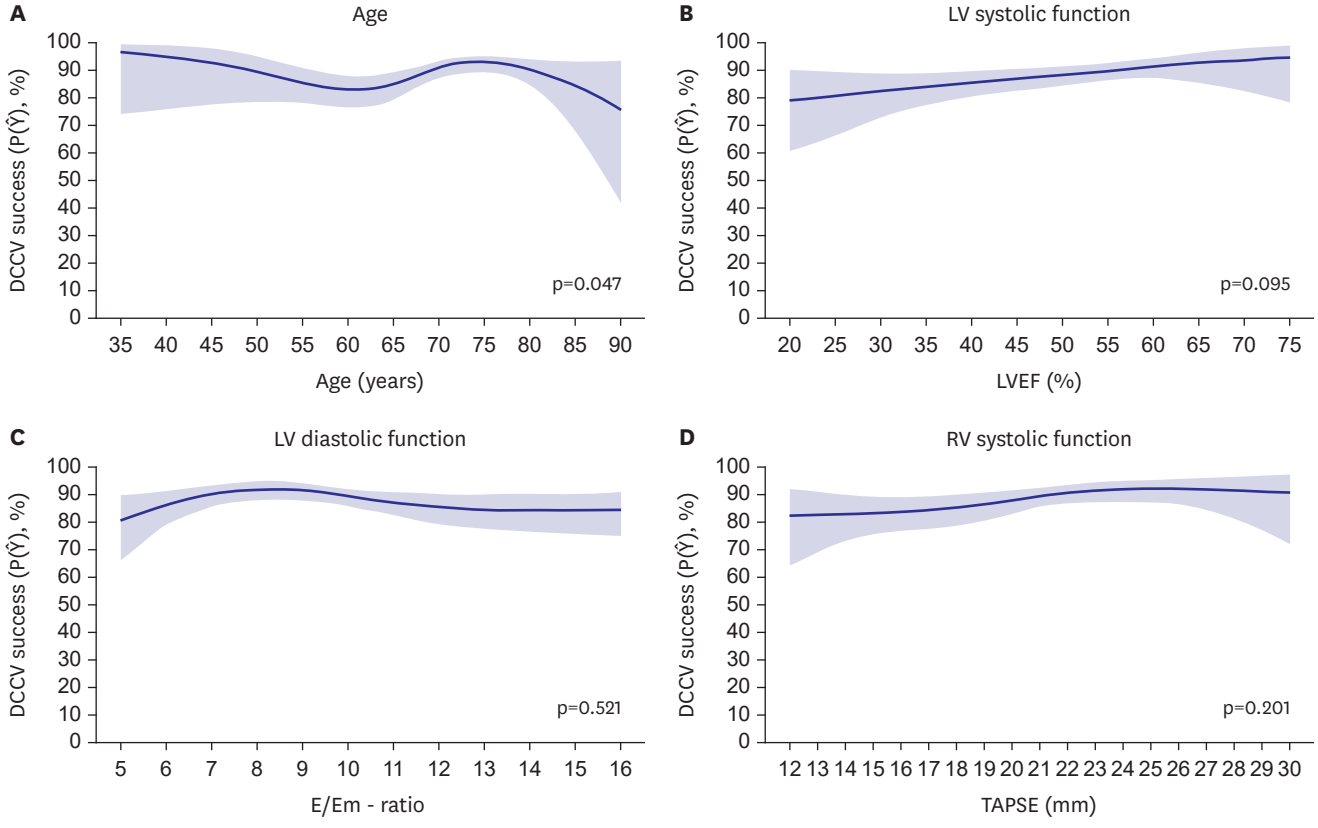

Figure 3. Overall and etiology-specific probability (P) of DCCV success as a function of age (A), LV systolic function (B), LV diastolic function (C), and RV systolic function (D).
DCCV = direct current cardioversion; E/Em = ratio of peak early diastolic filling (E) to early diastolic lateral mitral annular velocity (Em) (representative of the left ventricular filling pressure, i.e., diastolic function); EF = ejection fraction; LV = left ventricular; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

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Table 4. Interaction analysis of main clinical covariates with RA regarding a successful direct current cardioversion

Covariates	RA area index (cm^2/m^2, from 8 to 11)	Interaction
	OR (95% CI)	p value
LA volume index	0.28 (0.13–0.61)	0.813
Sex	0.29 (0.12–0.81)	0.331
LV dysfunction	0.27 (0.11–0.85)	0.856
RV dysfunction	0.29 (0.13–0.75)	0.094
Significant PH	0.22 (0.10–0.74)	0.901
Valve disease	0.21 (0.10–0.54)	0.745
Baseline AA medication	0.21 (0.11–0.73)	0.732

Interquartile range OR and 95% CI with lower and upper bound of RA area index as described in **Table 3**. Regressions and results are based on 5000 bootstrap repetitions.
AA = antiarrhythmic; CI = confidence interval; LA = left atrial; LV dysfunction = presence of a left ventricular ejection fraction <50%; PH = pulmonary hypertension defined as right ventricular systolic pressure >35 mmHg; OR = odds ratio; RA = right atrial; RV dysfunction = presence of a reduced tricuspid annular plane systolic excursion <16 mm.

Patients with an unsuccessful direct current cardioversion

Of the 66 patients with unsuccessful direct DCCV, 9 (14%) patients had failed DCCV without even one beat of sinus rhythm, and 57 (86%) patients experienced IRAF within the first minutes after DCCV. In comparison with patients with IRAF, patients with true DCCV failure were slightly older, used more often antiarrhythmic medication at baseline, and had more often positive cardiovascular risk factors, but higher LVEF. However, iRA area and iLAV were similar. A detailed summary of the main demographic, clinical and echocardiographic baseline characteristics of the two groups is provided in the supplementary data section (**Supplementary Table 1**).

DISCUSSION

The present study evaluated the role of indexed RA size in the immediate success of DCCV in patients with symptomatic persistent AF. The principal findings of this study can be summarized as follows: i) iRA area but not iLAV is a strong echocardiographic indicator of DCCV success; ii) CHD, female sex, and AF type are important clinical factors that influence DCCV success, suggesting a complex interaction with iRA area; iii) iRA area, but not iLAV, is associated with the AF duration of patients.

Although AF is a disease of the left atrium, recent studies revealed that RA size rather than LA size has a higher predictive power for early and midterm recurrence of AF after DCCV or after ablation of AF.[12-14)21)] It would therefore seem reasonable to assume that RA rather than LA size could influence the immediate outcome of DCCV. Indeed, from previous studies, LA size has only weak or no prognostic value, and RA size has not been thoroughly studied.[3)6)7)22)] In line with those reports, we demonstrated that clinical characteristics such as AF duration, sex, cardiovascular diseases, and medication intake might influence immediate DCCV success in persistent AF. But most importantly, our study revealed for the first time an independent and strong association between RA size and immediate DCCV outcome in these patients (**Figure 2**, **Table 1**). While both our study and the previous study by Luong and colleagues[13)] examined the outcome of DCCV in AF patients, our study had a larger sample size and focused on immediate DCCV success, while the previous study analyzed AF recurrence at 6 months after successful DCCV. These studies provide complementary insights into the success of DCCV in AF patients. The question arises as to how the relationship among the amount of RA size, epidemiology of AF and success of DCCV is interconnected. Of interest,

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Hocini and colleagues identified substrates in the right atrium requiring ablation to achieve AF termination in 20% of patients with persistent AF.[23] This finding inevitably suggests that the right atrium may also be subjected to the structural and electrical perturbations of AF progression.[10] In line with these observations, we demonstrated that RA but not LA enlargement correlated first with the duration/type of AF and second with the cumulative level of shock energy and increasing number of shock attempts during DCCV procedure (**Figure 1**). In addition, RA enlargement represents cardiac diseases other than AF. Heart failure due to CAD conditions not only influence LA but also RA remodeling and dysfunction by secondary pulmonary hypertension.[24][25] Since the underlying pathophysiology of AF is multifactorial, the high male prevalence in our study group reflects the gender-specific differences in AF epidemiology with well-established associations between CAD and cardiovascular risk factors, which could act as "perpetrators" of a successful DCCV.[26][27] While our study did not address the underlying mechanisms, previous research has explored the associations between RA size and AF risk.[11] However, further investigation is needed to fully understand this relationship.

Nevertheless, LA size (i.e., enlargement) remains a hallmark of AF as shown in our study population. Our patients revealed the amount of LA dilatation that was comparable to other studies[2][3][7] indicating an advanced level of LA electrical remodeling and, therefore, eventually extending to the right atrium.[28] This reflects the correlation we found with RA size and type of persistent AF, which means that RA dilatation may be a sign of progressive atrial cardiomyopathy or progression of underlying (electrical) disease. Although we did not detect higher-order interactions between anthropomorphic or clinical parameters with RA size and DCCV outcome (**Table 4**), the measures of association, while statistically not significant, remained remarkably stable for iLAV, sex, AF duration, and CHD in the full multivariable regression (**Table 1**). In our opinion, these results suggest a complex interaction between the above mentioned factors and RA enlargement. In other words, the right atrium might be considered as the ultimate or common patho-physiological pathway irrespective of an only AF or a concomitant non-AF related cardiac disease progression. This needs to be investigated in future studies, since our study was not designed to unveil the direct molecular, humoral, or electrical link between RA size and immediate DCCV success. However, we believe that our work may lay the groundwork for future studies to explore the intricate mechanisms of disease progression in AF involving the right atrium.

There are several limitations in this observational single-center study. First, there may be some bias in the patients referred for DCCV, as demonstrated by the inhomogeneous patient composition. However, the high male prevalence reflects the current epidemiological situation in AF.[27] Second, our study is limited by the use of RA area, which does not accurately reflect RA volume due to the complex geometry. Additionally, a more accurate measurement of RA volume using biplane or 3D echocardiography would be ideal, these methods require specialized skills and may not be feasible in larger studies. However, we demonstrated low inter-observer variability in RA area measurement (<10%) and support the use of indexed RA area in clinical practice. Third, although our study followed a strict protocol-based approach for the increase in DCCV energy. The DCCV procedure was performed at the discretion of the physician. However, we applied biphasic shock waves exclusively in the anterior-posterior position, which are independent of the transthoracic impedance and together result in high efficacy.[8][29][30] The good success rate of 89% in our study is in line with recent reports.[2-4] Fourth, this study only analyzed patients with persistent AF, and may not be applicable to patients with paroxysmal AF. Finally, our study was not

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designed for outpatient follow-up after successful DCCV, so we cannot draw conclusions about the role of RA size and recurrence of AF. In addition, we recommend considering the inclusion of tobacco or e-cigarette use in future studies, as these factors may potentially influence the risk of developing CHD and the outcome of interventions such as DCCV in AF. However, further studies with a broader collective of patients are needed to externally validate the present findings.

Our study demonstrated that iRA area may be a useful echocardiographic indicator of immediate success of direct DCCV in patients with AF. Importantly, this parameter has predictive value over iLAV.

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SUPPLEMENTARY MATERIALS

Supplementary Data 1

Supplementary methods.

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Supplementary Table 1

Main demographic, clinical and echocardiographic baseline characteristics of patients stratified by the type of unsuccessful direct cardioversion (n=66)

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Supplementary Figure 1

Online measurement of the RA area in end-systole from the RV-focused apical 4-chamber view. The RA area is represented by the blue curve going from the lateral to the septal tricuspid annulus at the insertion of interatrial/interventricular septum. This person had an averaged RA area of 19.3 cm2 and indexed to body surface area of 10.1 cm2/m2.

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Supplementary Figure 2

Upper panel shows the correlation plot of RA area measurements between two independent observers (1 and 2) with R as the Pearson's correlation coefficient R and corresponding significance value p. The dashed diagonal represents the line of identity.

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