When Cardioversion May Be Complicated

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ABSTRACT: **Background:** In recent years cardioversion of atrial fibrillation has become a routine procedure, enabling symptomatic functional improvement in most cases. However, some patients develop complications after cardioversion. Identifying these individuals is an important step toward improving patient outcome.

Objectives: To characterize those patients who may not benefit from cardioversion or who may develop complications following cardioversion.

Methods: We retrospectively analyzed 186 episodes of cardioversion in 163 patients with atrial fibrillation who were admitted to our cardiology department between 2008 and 2013 based on their clinical and echocardiographic data. Patients were divided into two groups: those with uncomplicated cardioversion and those who developed complications after cardioversion.

Results: Of the 186 episodes, cardioversion was completed in 112 men (60%) and 74 women (40%), $P < 0.00001$. Complications after cardioversion occurred in 25 patients (13%). These patients were generally older (72 vs. 65 years, $P < 0.01$), were more often diabetic (52% vs. 27%, $P = 0.005$), had undergone emergency cardioversion (64% vs. 40%, $P = 0.01$), had left ventricular hypertrophy (left ventricular mass 260 vs. 218 g, $P = 0.01$), had larger left atrium (left atrial volume 128 vs. 102 ml, $P < 0.009$), and more often died from complications of cardioversion (48% vs. 16%). They had significant mitral regurgitation (20% vs. 4%, $P = 0.03$) and higher pulmonary artery pressure (50 vs. 42 mmHg, $P < 0.02$).

Conclusions: People with complications after cardioversion tend to be older, are more often diabetic and more often have severe mitral regurgitation. In these patients, the decision to perform cardioversion should consider the possibility of complications.

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KEY WORDS: cardioversion, atrial fibrillation, complications of cardioversion

Normal left atrial contractions provide 15–20% of left ventricular filling and 10–15% of cardiac output [1]. Patients with chronic atrial fibrillation have worse functional class [2]. Some of these patients may benefit from cardioversion even if their ventricular function is preserved or normal. Atrial fibrillation in combination with congestive heart failure has a poor prognosis and an increased risk of death [3]. Atrial fibrillation is a known cause of stroke and systemic embolism, especially in older patients [4]. In patients with structural heart disease, valvular heart disease or left ventricular dysfunction, the input of left atrial contraction to ventricular filling and cardiac output is important, and these patients often undergo cardioversion even in the absence of symptoms. There are, however, patients who do not improve after cardioversion. Complications related to cardioversion can be divided into thromboembolic events, arrhythmias, and hemodynamic decompensation. Thromboembolic complications after cardioversion occur in 0.7% of patients [5] and are usually related to inadequate anticoagulation. Bradyarrhythmias were found to occur in 0.9% of electrical cardioversions, 44% of them needing permanent pacemaker insertion [6]. Pulmonary edema is a rare complication of cardioversion [7], as is profound hypotension [8], which is related to abrupt hemodynamic changes after the cardioversion. In this study we attempted to better define patients who might develop complications after cardioversion.

PATIENTS AND METHODS

We reviewed a digital database of patients with atrial fibrillation who were hospitalized in the cardiology department or were transferred from other departments and underwent cardioversion between 2008 and 2013. Patients who underwent cardioversion during admission to the internal medicine department were not included in this study. Clinical and echocardiographic data of these patients were reviewed and analyzed regarding cardiac risk factors (e.g., coronary artery disease, hypertension, diabetes mellitus, smoking), significant non-cardiac co-morbidities (e.g., cerebral vascular accident, Parkinson's disease, malignancy, Alzheimer's disease, muscular dystrophy), and outcome and complications rate. Echocardiographic examinations of these patients were reviewed and analyzed regarding left atrial size, left ventricular size and function, left ventricular hypertrophy (LVH), pulmonary artery pressure, and valvular abnormalities.

Our goal was to identify echocardiographic and clinical features of patients at higher risk for developing complications after cardioversion. We divided the patients into two groups: those with an uneventful course and those who developed complications after cardioversion. The group that experienced

complications was divided into two subgroups: those with serious life-threatening complications and those with less serious complications such as bradycardia, hypotension, renal failure, and apnea. All subjects were followed for up to 5 years. Since this retrospective study entailed no patient contact and patient identification numbers were not revealed or published, no informed consent was obtained. Digital files of available echocardiography results were analyzed. These exams were performed using echo systems (General Electric; Horten, Norway) (Vivid 9, Vivid 7, Vivid i, and Vivid 3) with a standard transducer 1.7–4 MHz. All examinations were interpreted by experienced physicians specializing in echocardiography. Linear echocardiographic measurements, left atrial volume and left ventricular (LV) mass were assessed according to standard recommendations [9,10]. Pulmonary artery systolic pressure was estimated according to current recommendations [11]. Although atrial fibrillation does not preclude assessment of diastolic function, these measurements are less accurate than in sinus rhythm and were not considered in this retrospective study.

STATISTICAL METHODS

Multivariate (MATLAB) analysis of variance (ANOVA) was applied to calculate complications and death rates according to echocardiographic and clinical parameters (ejection fraction, pulmonary artery pressure, severe mitral and aortic regurgitation), presence of LVH (left ventricular mass, interventricular septum thickness), left atrial size (diameter, area and volume), age, diabetes mellitus, renal failure, and urgency of cardioversion. These data are presented as a color coded model, where red is associated with the highest risk [Figure 1]. This color coded model was first used by Leitman et al. [12].

RESULTS

During the study period, 443 cardioversions for atrial fibrillation were performed at Assaf Harofeh Medical Center. Of these, 186 were performed in 163 patients admitted to the Department of Cardiology [Table 1]. Mean age was 66 years. There were 112 men (60%) and 74 women (40%), $P < 0.00001$. In 153 patients undergoing cardioversion, transthoracic echocardiography was performed during or close to the time of admission. These data were available for analysis in 82% of patients. Transesophageal echocardiography was performed in 60 cases (32%); other patients received optimal anticoagulation according to standard guidelines [13]. Of the 179 patients (96%) who underwent direct current shock (DC-shock), 4 received shocks from an implantable cardiac defibrillator (ICD), and the other 175 patients underwent external cardioversion. External direct current cardioversion was conducted under short general anesthesia using propofol, with 175 Joules (50–600 J) delivered at mean 1–2 DC shocks. In 118 patients (63%) anti-arrhythmic drugs were administered before electrical cardioversion, 89 (48%) received amiodarone, 23 (12%) were given 1C group drugs (fleacinide and propafenone), and for 6 patients group III medications such as sotalol and vernakalant were used. Pharmacological cardioversion was successful in seven patients (4%): four with amiodarone, two with vernakalant, one with sotalol. Emergency cardioversion was performed in 80 cases (43%).

Table 1. Demographic and clinical data of study patients

	Complicated	Uncomplicated	*P* value
No. of cardioversions	25 (13%)	161 (87%)	
Age, years	72 ± 10	65 ± 12	< 0.01
Internal medicine department*	15 [60%]	48 [30%]	0.001
Length of hospital stay, days	10 ± 5	5 ± 4	< 0.00001
Successful DC shock	21 [94%]	153 [95%]	0.16
Recurrent	10 [40%]	13 [8%]	0.002
Emergency DC shock	16 [64%]	64 [40%]	0.01
DC shock	24 [96%]	155 [96%]	0.9
Diabetes mellitus	13 [52%]	43 [27%]	0.005
COPD/asthma	6 [24%]	18 [11%]	0.07
CAD	7 [24%]	61 [38%]	0.3
Hypertension	14 [56%]	90 [56%]	1.0
Severe co-morbidities	6 [24%]	29 [18%]	0.5
TTE performed	22 [88%]	131 [81%]	0.4
TEE performed	8 [32%]	52 [32%]	1.0
Previous PAF	15 [60%]	85 [53%]	0.5
Death (long term)	12 [48%]	26 [16%]	< 0.005

*Some people were transferred from the cardiology department to the internal medicine department based on medical indications for recovery, occurring more often in patients with complications
DC shock = direct current shock, AF = atrial fibrillation, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, CAD = coronary artery disease, TTE = transthoracic echocardiography, TEE = transesophageal echocardiography, PAF = paroxysmal atrial fibrillation.

The total complication rate was 13% (25 patients). Complications included respiratory failure, bradycardia, hypotension, ventricular arrhythmia, renal and hepatic failure, and death. These 25 patients were older (72 vs. 65 years old, $P < 0.01$), more often diabetic (52% vs. 27%, $P = 0.005$), had more recurrent episodes of atrial fibrillation during the hospitalization, and more often underwent emergency cardioversion (64% vs. 40%, $P = 0.01$).

Stroke risk was calculated according to the CHA_2DS_2-VASc score for each group of patients. In the group of patients with uncomplicated cardioversion risk of stroke, according to the CHA_2DS_2-VASc assessment tool, the score was 2.8 vs. 3.5, $P = 0.06$ in the group of patients with complicated cardioversion. International normalized ratio (INR) at the time of cardioversion was 2.1 ± 0.9 vs. 2 ± 0.9, $P = 0.6$, in uncomplicated cardioversion vs. patients with complications.

There was no significant difference in the ejection fraction between the two groups of patients (49 vs. 45%, $P = 0.2$) [Table 2].

Table 2. Echocardiographic characteristics

	Complicated	Uncomplicated	*P* value
EF, %	45 ± 16	49 ± 12	0.17
LVEDD, cm	5.3 ± 1	5 ± 0.9	0.18
LVESD, cm	3.6 ± 1.2	3.3 ± 1	0.28
IVS, cm	1.4 ± 0.3	1.2 ± 0.3	< 0.04
LVm, g	260 ± 76	218 ± 71	0.01
PW, cm	1.1 ± 0.2	1.1 ± 0.2	0.7
LAD, cm	4.7 ± 0.7	4.4 ± 0.6	< 0.03
LAA, cm^2	32 ± 6	28 ± 7	0.01
LAv, ml	128 ± 38	102 ± 41	< 0.009
PAP, mmHg	50 ± 17	42 ± 14	< 0.02
Severe MR	5 [20%]	6 [4%]	0.03
Severe MS	0	3	NA
Severe AI	1	0	NA
Severe AS	3 [12%]	3 [2%]	NA

EF = ejection fraction, LVEDD = left ventricle end-diastolic diameter, LVESD = left ventricle end-systolic diameter, IVS = interventricular septum, LVm = left ventricular mass, PW = posterior wall, LAD = left atrial diameter, LAA = left atrial area, LAv = left atrial volume, PAP = pulmonary artery pressure, MR = mitral regurgitation, MS = mitral stenosis, AI = aortic insufficiency, AS = aortic stenosis, NA = not applicable

Patients in the complications group had thicker interventricular septum (1.4 vs. 1.2 cm, $P < 0.04$) and higher left ventricular mass (260 g vs. 218 g, $P = 0.01$). In 154 patients (83%) we found larger left atrial diameter (4.7 vs. 4.4 cm, $P < 0.03$; area 32 vs. 28 cm^2, $P = 0.01$) and volume (128 vs. 102 ml, $P < 0.009$). In 134 patients (72%) we found higher pulmonary artery pressure (50 vs. 42 mmHg, $P < 0.02$) and often more significant mitral regurgitation (20% vs. 4%, $P = 0.03$).

Patients were monitored for 1 to 5 years [Table 1]. Patients in the complicated group had a higher total mortality rate (48% vs. 16%, $P < 0.005$) during the study period; seven of them (58%) died during the current hospitalization.

Table 3 details the patient data. Thirteen patients (cases 1–13) in the complicated group demonstrated severe complications that required intensive intervention. After cardioversion, 4 of 13 patients suffered multi-organ failure (cases 1, 2, 3, 10). One patient (case 5) with severe mitral regurgitation was referred for mitral valve surgery when his heart failure worsened due to bradycardia and atrioventricular block after cardioversion. A 69 year old woman (case 10) was admitted to the hospital with rapid atrial fibrillation 12 days after transcatheter aortic valve implantation (TAVI). After cardioversion she experienced hemodynamic and respiratory deterioration with intractable heart failure. Repeat echocardiography, including transesophageal echocardiography (TEE), revealed a perivalvular aortic valve leak that appeared severe while in sinus rhythm. Surgery was not recommended, and the patient died.

Patient 12 required mechanical ventilation after cardioversion; pulmonary embolism was diagnosed later by computed tomography (CT) angiography. This patient survived for 4 years.

In the group with less serious complications [Table 3, cases 14–25], renal function deteriorated in two patients, and in one patient acute tubular necrosis was confirmed by kidney scan. Six patients developed bradycardia, and three of them were referred for pacemaker implantation. Three patients developed hypotension (two due to amiodarone) and one had hypoventilation with apnea and profound desaturation.

MULTIVARIATE ANALYSIS

Multivariate analysis [Figure 1] showed that the strongest independent predictor of any complications and death during the hospitalization was severe valvular mitral or aortic regurgitations, followed by pulmonary artery hypertension. Pulmonary hypertension in combination with diabetes and emergency cardioversion was associated with a 60% risk of any complication and was predictive for severe complications in 50% of patients. Pulmonary hypertension associated with LVH was a predictor of severe complications in 50%. LVH in patients with diabetes was predictive for severe complications in 42%. Left ventricular dysfunction (EF < 40%) was not an independent predictor of complications, but when associated with pulmonary hypertension it was a predictor of complications in 50%. The strongest independent predictor of death after cardioversion was severe valvular regurgitations (25%), followed by pulmonary hypertension (21%). In association with LVH, valvular regurgitations increased risk of in-hospital mortality by up to 40%. This risk was increased when pulmonary hypertension was associated with reduced ejection fraction (30%) or with diabetes (31%). Emergency cardioversion in diabetic patients with moderate LV dysfunction was associated with a 27% risk of in-hospital mortality; in patients with recurrent atrial fibrillation and LV dysfunction (EF < 40%) it was predictive for a 36% death rate during hospitalization.

DISCUSSION

Cardioversion is associated with a risk of thromboembolism and stroke [5] that can usually be lowered with appropriate anticoagulation and adherence to clinical guidelines [13]. Other complications are rare, but few clinical studies on this topic have been performed. To the best of our knowledge, only 30 cases of pulmonary edema after cardioversion have been reported in the English-language medical literature since 1965, and 93% of these cases occurred after the cardioversion of atrial fibrillation and flutter [14]. Transient deterioration of left ventricular ejection fraction was found in patients with systolic dysfunction after electrical shock with defibrillator and deterioration of diastolic function after defibrillation irrespective of baseline ejection fraction [15]. Al-Halawani et al. [16] described a unique case of Ogilvie's syndrome, a pseudo-obstruction of

Table 3. Patients with complications after cardioversion

	Case no.	Age/ gender	Co-morbidities	Urgency	Duration of AF	Complication	Died	Died during hospitalization	PAP, mmHg	Severe AI	Severe MR	LAA cm²	LAD, cm	IVS, cm	EF, %
Severe complications	1	86/F	HOCM	1	Unknown	Respiratory failure, multi-organ failure	1	1	70	–	–	43	4.7	20	70
	2	87/F	DM, hypertension, moderate-severe MR	–	1 year	Pulmonary edema, multi-organ failure, bradycardia, hypotension	1	1	60	–	1	37	4.4	1.5	60
	3	62/M	Severe MR	1	‹ 24 hours	Pulmonary edema, multi-organ failure, shock, bradycardia	1	1	90	–	1	35	6.8	1.7	25–30
	4	74/M	CHF, CAD, admitted with CVA	1	Hours	Septic shock	1	1	–	–	–	38	4.1	0.9	35
	5	72/M	RF, DM, hypertension, significant MR	1	‹ 2 weeks	Respiratory failure, bradycardia and AV block	1	–	55	–	1	31	4.6		55
	6	78/F	DM, severe AS, severe COPD	1	2 days	Arrythmia, multifocal atrial tachycardia	1	1	55	–	–	29	4	1.4	25
	7	61/M	Hypertension, DM, SSS	1	‹ 3 days	Torsade de pointes VT due to bradycardia	–	–	30	–	–	25	4.5	1.3	50
	8	51/M	OSA, COPD, obesity	–	14 days	Pulmonary edema	–	–	37	–	–	39	5.2	1.3	30
	9	83/F	DM, hypertension, RF, S/P Ca of ovaries and uterus	1	1 month	Respiratory failure	1	–	60	–	–	28	5.2	1.4	45–50
	10	69/F	S/P MVR, S/P CVA, recent TAVI, myeloproliferative disorder	–	1 day	Respiratory failure, multi-organ failure	1	1	80	1	–	30	5.9	1.3	60
	11	52/M	DM, hypertension, S/P MI, S/P CABG and MV repair	1	Hours	Sudden death	1	1	55	–	–	31	4.6	1.5	25
	12	81/F	DM	1	Hours	Respiratory failure, pulmonary embolism	1	–	37	–	–	27	4.3	1	40
	13	71/F	Hepatitis C, hypertension, DM, hypertrophic CMP	–	3 months	Sudden death due to torsade de pointes	1	–	40	–	–	41	4.9	1.6	› 65
ess severe complications	14	63/M	S/P CABG and MV repair, severe MDS, S/P lymphoma and chemotherapy	–	11 days	Acute tubular necrosis	–	–	70	–	–	36	5.1	1.4	Mild dysfunction
	15	84/M	DM, hypertension, RF	1	Unknown	Bradycardia, hypotension, permanent pacemaker	–	–	40	–	–	29	4.4	1.4	40–45
	16	82/F	HOCM, ulcerative colitis, severe AS, moderate + MR	1	‹ 1 month	Transient renal and hepatic failure due to hypotension after DC	–	–	45	–	1	29	5	1.9	› 65%
	17	75/M	Hypertension, s/p CABG	–	3 weeks	Syncope with bradycardia	–	–	40	–	–	38	4.7	1.2	50–55
	18	77/F	Acute myocarditis, schizophrenia	1	Hour	Profound hypotension	–	–	40	–	–	23	3.6	1.2	60
	19	60/M	DM, severe COPD, obesity, hypertension	–	8 months	Respiratory failure	–	–	–	–	–	–	–	–	–
	20	69/M	Hypertension, S/P AF ablation	–	1 month	Bradycardia, hypotension	–	–	35	–	–	36	5.3	1.4	50–55
	21	73/M	Hypertension, CAD	–	‹ 24 hours	Bradycardia	–	–	–	–	–	–	–	–	–
	22	70/M	Ischemic CMP, ICD, severe MR	1	Unknown	Profound hypotension	–	–	35	–	1	37	4.7	0.8	20
	23	85/F	Anterior MI, DM, hypertension, moderate-severe AS	1	Hours	Hypotension	–	–	55	–	–	23	4.1	1.1	30
	24	60/F	OSA, cerebral paralysis	1	‹ 1 year	Bradycardia, nodal rhythm, permanent pacemaker	–	–		–	–	–	–	–	–
	25	76/M	DM, hypertension, COPD, S/P CABG, S/P MI	1	Hours	Extreme bradycardia	1	–	35	–	–	23	4.1	1.2	35

AF = atrial fibrillation, PAP = pulmonary artery pressure, AI = aortic insufficiency, MR = mitral regurgitation, LAA = left atrial area, LAD = left atrial diameter, IVS = interventricular septum, EF = ejection fraction, HOCM = hypertrophic obstructive cardiomyopathy, DM = diabetes mellitus, CHF = congestive heart failure, CAD = coronary artery disease, CVA = cerebrovascular accident, RF = renal failure, AS = aortic stenosis, COPD = chronic obstructive pulmonary disease, SSS = sick sinus syndrome, OSA = obstructive sleep apnea, Ca = carcinoma, MVR = mitral valve replacement, TAVI = trans-aortic valve implantation, CABG = coronary artery bypass grafting, CMP = cardiomyopathy, ICD = implantable cardioverter defibrillator, MI = myocardial infarction, S/P = sensory problem

Figure 1. Predictors of severe complications after cardioversion
Multivariate analysis results with $P < 0.05$

The strongest independent predictor of severe complications after cardioversion is severe left-sided regurgitation and pulmonary hypertension. Pulmonary hypertension in combination with LVH and diabetes is associated with the highest risk of severe complications.

Color code: **Red** = risk of severe complications (≥ 40%); **Orange** = risk of severe complications after cardioversion (30–39%); **Blue** = risk of severe complications after cardioversion (20–29%); **Green** = risk of severe complications (10–19%); **White** = there is a low number of these cases (< 10)

	Sev Reg	PAP > 50	RF	DM	Age ≥ 69	Urgent	EF < 40	IVS > 1.4	LAA > 32	LAD > 4.7	LVm > 230	LAV > 120
Sev Reg	33% $P = 0.0002$											30% $P = 0.005$
PAP > 50		28% $P < 0.0001$		46%* $P < 0.00001$	29% $P = 0.0002$	33% $P < 0.00001$	30% $P = 0.009$	50% $P < 0.00001$	23% $P = 0.04$	31% $P = 0.001$	38%** $P < 0.00001$	31% $P = 0.0003$
RF			20% $P = 0.04$							27% $P = 0.02$		
DM		46%* $P < 0.00001$		16% $P = 0.001$	21% $P = 0.002$	21% $P = 0.0005$		42% $P < 0.00001$		40% $P = 0.0002$	29% $P = 0.0008$	
Age ≥ 69		29% $P = 0.0002$		21% $P = 0.002$		15%*** $P = 0.02$		25% $P = 0.01$	20% $P < 0.05$			25% $P = 0.001$
Urgent		33% $P < 0.00001$		21% $P = 0.0005$	15%*** $P = 0.02$	11% $P < 0.05$					21% $P = 0.008$	
EF < 40		30% $P = 0.009$							25% $P = 0.04$		21% $P = 0.03$	25% $P = 0.02$
IVS > 1.4		50% $P < 0.00001$		42% $P < 0.00001$	25% $P = 0.01$			19% $P = 0.02$		23% $P < 0.05$		33% $P = 0.0004$
LAA > 32		23% $P = 0.04$			20% $P < 0.05$		25% $P = 0.04$		17% $P < 0.05$			
LAD > 4.7		31% $P = 0.001$	27% $P = 0.02$	40% $P = 0.0002$				23% $P < 0.05$				
LVm > 230		38%** $P < 0.00001$		29% $P = 0.0008$		21% $P = 0.008$	21% $P = 0.03$					
LAV > 120	30% $P = 0.005$	31% $P = 0.0003$			25% $P = 0.001$		25% $P = 0.02$	33% $P = 0.0004$				18% $P = 0.004$

*PAP > 50 + DM + Urgent = 50% risk of severe complications,

**PAP > 50 + Urgent + LVm>230 predicts 55% risk of severe complications, $P < 0.00001$,

***Age > 69 + Urgent + LVm > 230 g predicts 27% risk of severe complications

Sev Reg = severe mitral and aortic regurgitation, PAP = pulmonary artery pressure, mmHg, RF = renal failure, DM = diabetes mellitus, IVS = interventricular septum, LAA = left atrial area, LAD = left atrial diameter, LVm = Left ventricular mass, LAV = Left atrial volume

the colon after cardioversion for atrial fibrillation. In our study, we attempted to define clinical and echocardiographic predictors for hemodynamic complications following cardioversion of atrial fibrillation.

We found 25 cases of deterioration following cardioversion [Table 3]. Thirteen patients had serious complications; most of them needed mechanical ventilation and seven died during the procedure. Pulmonary embolism, as occurred in case 12 [Table 3], was recently observed in 2 of 38 episodes of thromboembolism after cardioversion [13]. In case 10 of our retrospective study, hemodynamic deterioration developed after cardioversion in the patient due to a severe aortic perivalvular leak. Rapid atrial fibrillation was a protective mechanism in this case, although sinus rhythm aortic regurgitation worsened and this patient eventually died from intractable heart failure and multi-organ failure. One month before undergoing TAVI, this woman underwent cardioversion without complications; her most serious problem was severe aortic stenosis.

In patients 7 and 13, polymorphic ventricular tachycardia was the cause of deterioration after cardioversion, and bradycardia may have caused the arrhythmia in one patient. In the group with less severe complications [Table 3], post-cardioversion bradycardia and/or hypotension were also frequent. Some of these complications may have been fatal had they occurred outside of the hospital setting. Two patients had deterioration in renal function that was thought to be due to low perfusion (in one, acute tubular necrosis was confirmed by kidney scan), although cholesterol emboli around the cardioversion could not be excluded. In our subjects, the only case with severe aortic regurgitation was due to a perivalvular leak in a patient after TAVI [Table 3, case 10].

In patients with severe left-side valvular regurgitation, higher ventricular response of atrial fibrillation is crucial for maintaining cardiac output. These patients are less sensitive to the loss of atrial contraction. Larger left atrial size is explained by more advanced remodeling and fibrosis of the atrium and is associated with less effective atrial contraction when sinus rhythm is restored.

Diastolic dysfunction is associated with left ventricular hypertrophy [17] and with diabetes mellitus [18]. The high prevalence of left ventricular hypertrophy and diabetes in the group of patients with complications is not surprising since

rapid heart rate during atrial fibrillation/flutter is a compensatory mechanism. The health of these patients tends to deteriorate following a sudden decrease in heart rate after the cardioversion, despite the theoretical advantage of restoration of normal atrial activity. Their left atrium is often enlarged, stunned and remodeled, and has undergone fibrosis. Atrial contraction of this atrium is not effective. After cardioversion, the heart rate slows and the left ventricular end-diastolic pressure rises; the left atrial contractile function recovers later than the right, which may explain the preferential increase in blood flow to the lungs and pulmonary edema [14,19,20].

Gomaa et al. [21] found that the electric current may directly injure the endothelial cells of the pulmonary capillaries, which may result in increased permeability of the pulmonary bed and may facilitate pulmonary edema [21].

In a recent study, Gillinov and colleagues [22] reported a lower rate of postoperative complications after cardioversion due to atrial fibrillation. They also found that all patients had a new atrial fibrillation, and since they were after coronary artery bypass surgery or valve replacement/repair, significant valvular abnormalities were not noted.

Furthermore, patients with complications were younger (mean age 68 vs. 72 years) in our study. Although ejection fraction and pulmonary artery pressure were not reported, those patients who had all undergone revascularization and/or valvular surgery appeared to be in better medical condition than our group of patients with complications.

We report the results of a selected high-risk group of patients who were primarily admitted to a hospital for cardioversion. Prevalence of emergency cardioversion in patients with complications (64%) is related to their outcome. Every third patient with moderate pulmonary hypertension who has undergone emergency cardioversion is at risk for serious complications. In our study, there were no cases of stroke due to adherence to the current recommendations on cardioversion in our department [5]. Even uncomplicated cases in our study had lower EF than did those evaluated by Iakobishvili et al. [23] in which 24 patients underwent elective cardioversion (49 vs. 52%, respectively).

Several mechanisms may explain hemodynamic and respiratory deterioration after cardioversion:

- Diastolic dysfunction due to older age, diabetes mellitus, and LVH, which are all potential predictors for the increased sensitivity for sudden decrease in heart rate after cardioversion
- Larger left atrial size with more advanced remodeling and more fibrosis that may result in permanent left atrial dysfunction, which in combination with cardioversion-induced atrial stunning [24] may lead to non-effective atrial function despite restoration of sinus rhythm
- In severe valvular mitral and/or aortic regurgitation, higher heart rate during atrial fibrillation is a protective mechanism to maintain cardiac output. Restoration of sinus rhythm after cardioversion cannot compensate for the sudden decrease in heart rate after cardioversion, and these patients often deteriorate
- Pulmonary hypertension is a marker for heart failure, pulmonary frailty, and diastolic dysfunction, and is a predictor for complications after cardioversion.

LIMITATIONS

All the risk factors predictive of a complicated course after cardioversion are also markers of morbidity and other complications with harmful a priori predictors. Our retrospective study was not designed to recommend against cardioversion in high-risk patients.

CONCLUSIONS

Older patients with diabetes, and those with severe valvular regurgitation, left atrium enlargement, left ventricular hypertrophy and pulmonary hypertension are all prone to hemodynamic and respiratory complications after cardioversion. A relatively rapid heart rate during atrial fibrillation is often protective in these subjects. The decision to perform cardioversion should not be taken lightly. Efforts should be make to maintain adequate heart rate after the procedure.

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Capsule

Chromatin state dictates drug response

Drugs inhibiting the phosphoinositide-(3)-kinase (PI3K) signaling pathway are effective in a subset of breast cancer patients. Tumors become resistant to these drugs; however, and this transition is often accompanied by increased transcription of genes regulated by the estrogen receptor. A better understanding of the mechanism linking PI3K signaling and estrogen receptor activity could potentially suggest strategies to prevent drug resistance. Toska et al. found that PI3K inhibition activates a specific epigenetic regulator, the histone methyltransferase KMT2D. The protein modifications catalyzed by KMT2D create a more open chromatin state, which unleashes estrogen receptor-dependent transcription. Thus, combination therapies consisting of PI3K inhibitors and KMT2D inhibitors may be more effective than PI3K inhibitors alone.

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Eitan Israeli

Capsule

JNK1 negatively controls antifungal innate immunity by suppressing CD23 expression

Opportunistic fungal infections are a leading cause of death among immune compromised patients, and there is a pressing need to develop new antifungal therapeutic agents due to toxicity and resistance to the antifungal drugs currently in use. Although C-type lectin receptor and Toll-like receptor-induced signaling pathways are key activators of host antifungal immunity, little is known about the mechanisms that negatively regulate host immune responses to a fungal infection. Zhao et al. found that JNK1 activation suppresses antifungal immunity in mice. They showed that JNK1-deficient mice had a significantly higher survival rate than wild-type control mice in response to *Candida albicans* infection, and the expression of JNK1 in hematopoietic innate immune cells was critical for this effect. JNK1 deficiency leads to significantly higher induction of CD23, a novel C-type lectin receptor, through NFATc1-mediated regulation of the CD23 gene promoter. Blocking either CD23 upregulation or CD23-dependent nitric oxide production eliminated the enhanced antifungal response found in JNK1-deficient mice. Notably, JNK inhibitors exerted potent antifungal therapeutic effects in both mouse and human cells infected with *C. albicans*, indicating that JNK1 may be a therapeutic target for treating fungal infection.

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Eitan Israeli

"Perhaps travel cannot prevent bigotry, but by demonstrating that all peoples cry, laugh, eat, worry, and die, it can introduce the idea that if we try and understand each other, we may even become friends"

Maya Angelou (1928–2014), American poet, memoirist, and civil rights activist