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Change in myocardial function after resuscitated sudden cardiac arrest and its impact on long-term mortality and defibrillator implantation

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ABSTRACT

Background: The impact of left ventricular ejection fraction (LVEF) changes after sudden cardiac arrest (SCA) on implantable defibrillator (ICD) utilization and long-term survival is not known. We therefore evaluated the influence of LVEF on these parameters in SCA survivors.

Methods: Data were collected on consecutive SCA survivors who had ≥ 1 echocardiogram after SCA and who survived to hospital discharge ($n = 655$). The median time from baseline to first follow-up echocardiogram was 162 days. LVEF $\geq 50\%$ was defined as normal. Patients were classified into 4 groups according to baseline (LVEFb) and follow-up (LVEFf) myocardial function: normal LVEFb and LVEFf (group 1, $n = 261$); reduced LVEFb and normal LVEFf (group 2, $n = 104$); normal LVEFb but reduced LVEFf (group 3, $n = 41$); and reduced LVEFb and LVEFf (group 4, $n = 249$). All-cause mortality and time to ICD implantation were examined in all groups.

Results: Over a median follow up of 4.3 years, death occurred in 279 (42%) of patients. Compared with patients in group 1, patients with any reduced LVEF at any time (groups 2–4) had significantly higher mortality, even after adjusting for unbalanced covariates (HR = 1.44, 95.0% CI 1.05–1.95, $p = 0.022$). ICDs were most commonly implanted in patients with persistently reduced LVEF (group 4: HR = 1.72, 95% CI = 1.26–2.35, $p = 0.001$).

Conclusion: We demonstrate that, in survivors of SCA, a reduced LVEF at or after the index event is associated with higher mortality but that patients with persistently reduced LVEF were most likely to receive ICD therapy. These findings have implications on the management of SCA survivors.

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The annual incidence of sudden cardiac arrest (SCA) in the United States is estimated to be about 350,000 for out-of-hospital and 209,000 for in-hospital cardiac arrest [1]. Survival after SCA remains poor. The CARES registry [2] reports that only 10.8% of patients survive to hospital discharge after non-traumatic out-of-hospital SCA compared to 25.8% for the in-hospital setting. In addition, SCA is associated with significant cardiac morbidity with an estimated 73% of survivors receiving a new cardiac diagnosis within the first year after the index event [3].

Reversible myocardial dysfunction has been previously reported in survivors of SCA [4,5] with contradictory impact on long-term prognosis [6,7]. Many suspected mechanisms have been

implicated in reversible myocardial dysfunction after SCA, including ischemia and reperfusion injury, inflammatory cardiac dysfunction, and catecholamine induced cardiac dysfunction among others [8]. The long-term sequelae of early myocardial injury during SCA and changes in myocardial function over time on long-term survival remain however poorly defined.

We therefore evaluated, in the present study, the association of baseline left ventricular ejection fraction (LVEF) and its change with long-term mortality and the likelihood of receiving an implantable cardioverter-defibrillator (ICD) in a large dataset of survivors of SCA.

1. Methods

1.1. Study design

We conducted a retrospective cohort analysis of all adults who survived SCA who were admitted to the University of Pittsburgh

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Medical Center hospitals between 2002 and 2012. This study was approved by the institutional review board of the University of Pittsburgh. SCA was defined as any patient admitted with a primary International Classification of Disease, 9th edition, Clinical Modification diagnostic code of ventricular fibrillation (427.41), ventricular flutter (427.42), ventricular tachycardia (427.1), or cardiac arrest (427.5).

Electronic medical records of 1433 patients who met the above inclusion criteria were reviewed to abstract clinical, demographic, laboratory, electrocardiographic, and echocardiographic data. All quantitative variables were collected at the initial time of admission for the index SCA. Patients who had 1 or more echocardiographic studies after the SCA event were included in the present analysis. Transthoracic echocardiogram reports were used to collect data on LVEF. Patients' initial echocardiogram after aborted SCA was used to quantify baseline LVEF (LVEFb) which was classified as normal ($\geq 50\%$) or reduced ($< 50\%$). Subsequent LVEF (LVEFf) was evaluated and also classified as normal ($\geq 50\%$) or reduced ($< 50\%$). The median time between baseline and follow-up echocardiogram was 162 (interquartile range 42–555) days. Patients were classified into 4 groups based on their baseline and follow-up LVEF: normal LVEFb and LVEFf (group 1, $n = 261$); reduced LVEFb and normal LVEFf (group 2, $n = 104$); normal LVEFb but reduced LVEFf (group 3, $n = 41$); and reduced LVEFb and LVEFf (group 4, $n = 249$).

Patients were followed to the end-point of death or last follow-up through February 20, 2017. The primary outcome of this analysis was all-cause mortality, which was ascertained through querying the electronic medical records and the social security death index using the updated Social Security Administration Death Master file, for which our health-care system is exempt from the three-year delay period by the Social Security Administration. The time to ICD implantation was examined as a secondary endpoint.

1.2. Statistical analysis

Categorical variables are presented as frequencies (percentages) and compared between groups using the chi-square test. Continuous variables are presented as mean $\pm$ standard deviation and compared using the analysis of variance test or its non-parametric equivalent, as appropriate. Survival curves were created using the Kaplan Meier method for patients in the 4 groups and compared using the log rank test. Adjustment for unbalanced covariates between the groups was done using Cox proportional Hazards multivariable models. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed on SPSS version 25.0 (IBM Inc., Armonk, NY).

2. Results

From the 1433 patients initially included in the study population, follow-up echocardiograms were available for 655 patients who constituted the study cohort (Fig. 1). Of these patients, 302 (46%) patients had a normal LVEF at baseline, of whom the majority ($n = 261$, 86%) continued to have a normal LVEF during follow-up (group 1) while the remaining patients ($n = 41$, 14%) experienced a decline in their LVEF (group 3). Baseline LVEF was reduced in 353 patients, of whom a minority ($n = 104$, 29%) had an improvement in LVEF during follow-up (group 2) while the remaining patients ($n = 249$, 71%) continued to have a reduced LVEF (group 4).

Table 1 shows the baseline characteristics of SCA survivors by LVEF group. Baseline demographics were comparable between the 4 groups. Patients with normal LVEF at baseline and during follow-up (group 1) had shorter QRS and QTc intervals on the surface electrocardiogram and were less likely to have a myocardial infarction or ischemia at the time of SCA. Patients with normal

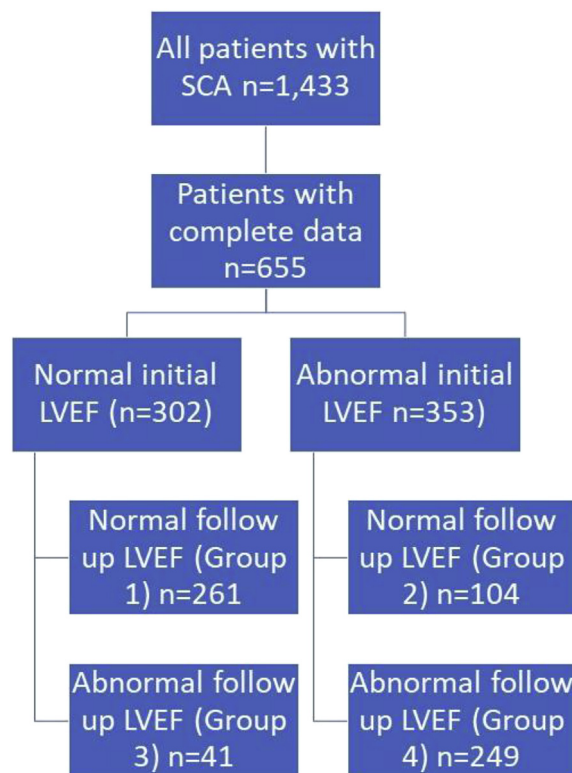


Fig. 1. Study population selection and classification.

baseline LVEF (groups 1 and 3) had a marginally higher baseline serum bicarbonate levels of unclear clinical significance. Patients with reduced LVEF at baseline and in follow-up (group 4) were more likely than other patients (groups 1–3) to receive an ICD after the index SCA. Importantly, there were no differences between the 4 groups in the presenting rhythm (ventricular tachycardia or ventricular fibrillation versus asystole or pulseless electrical activity) or in the location of the SCA (out-of-hospital versus in-hospital).

Our primary end-point of mortality was reached in 38.7%, 45.2%, 51.2% and 43.8% in group 1 through 4, respectively. Fig. 2A shows the time to death by LVEF groups. There was a trend for better survival in patients who had a normal LVEF at baseline and in follow-up (group 1) compared to all the other groups. In fact, compared to patients who had a normal baseline LVEF who experienced decline in myocardial function overtime (group 3), patients who had a normal LVEF at baseline and in follow-up (group 1) had a significantly better survival (HR = 1.61, 95% CI 1.00–2.58, $p = 0.048$). Compared to patients who had a documented reduced LVEF at baseline or in follow-up (groups 2–4), patients in group 1 had significantly better survival after adjusting for all unbalanced covariates (HR = 1.44, 95% CI = 1.05–1.95, $p = 0.022$, Table 2, Fig. 2B).

The time to ICD implantation was also examined by LVEF group. Patients who had a reduced LVEF at baseline and in follow-up (group 4) were significantly more likely than patients in other groups (groups 1–3) to be implanted with an ICD after SCA (HR = 1.72, 95% CI = 1.26–2.35, $p = 0.001$, Fig. 3).

3. Discussion

We examined the association between patterns of LVEF change after SCA and long-term mortality and ICD therapy. Our data demonstrate that patients with normal LVEF at baseline after SCA

Table 1
Baseline characteristics of sudden cardiac arrest survivors by LVEF group.

Variable	Group 1(n = 261)	Group 2(n = 104)	Group 3(n = 41)	Group 4(n = 249)	P- value
DEMOGRAPHICS					
Age (years)	61.3 ± 15	61.4 ± 16.8	64.5 ± 15.6	62.6 ± 15.2	0.54
BMI (kg/m ²)	29.9 ± 7.8	28 ± 5.4	30.6 ± 6.1	30.5 ± 8.5	0.06
Female Gender	111(40%)	39(14%)	20(7%)	104(38%)	0.64
Race					0.45
White	216(83%)	91(87%)	34(83%)	214(86%)	
Black	32(12%)	12(12%)	5(12%)	25(10%)	
Other	13(5%)	1(1%)	2(5%)	10(4%)	
LOCATION					
In-hospital	152(58%)	57(55%)	30(73%)	128(51%)	0.2
Out-of-hospital	109(42%)	47(45%)	11(27%)	121(49%)	
INITIAL RHYTHM					
VT/VF	150(57%)	61(59%)	25(61%)	150(60%)	0.51
PEA/Asystole	111(43%)	43(41%)	16(39%)	99(40%)	
VITAL SIGNS					
Systolic blood pressure	127 ± 32	123 ± 34	123 ± 30	125 ± 32	0.67
Diastolic blood pressure	70 ± 20	69 ± 21	64 ± 20	70 ± 22	0.30
ECC					
Ventricular rate	89 ± 28	91 ± 24	88 ± 30	89 ± 23	0.89
PR interval (ms)	172 ± 45	159 ± 33	177 ± 50	168 ± 38	0.68
QRS duration (ms)	103 ± 27	109 ± 31	114 ± 48	110 ± 31	0.02
QT (ms)	399 ± 81	397 ± 65	403 ± 89	407 ± 69	0.62
QTc (ms)	469 ± 56	480 ± 66	479 ± 71	481 ± 53	0.10
BIOCHEMICAL MARKERS					
Troponin (μg/L)	10.75 ± 47.34	6.95 ± 23.78	10.53 ± 33.53	8.31 ± 34.93	0.85
CK-MB (μg/L)	46.5 ± 96.2	55.9 ± 100.6	27.8 ± 68.7	60 ± 138.7	0.77
Serum potassium level (mg/dL)	4.3 ± 1	4.1 ± 0.8	4 ± 0.8	4.1 ± 1	0.51
Serum magnesium level (mg/dL)	2.0 ± 0.5	2.0 ± 0.5	2.0 ± 0.4	2.0 ± 0.5	0.97
Serum bicarbonate level (mmol/L)	24 ± 5	22 ± 5	24 ± 7	23 ± 5	0.02
Atrial fibrillation	85(33%)	27(26%)	15(37%)	69(30%)	0.33
Myocardial infarction or ischemia	99(40%)	45(43%)	21(51%)	119(48%)	0.02
Diabetes mellitus	81(31%)	36(35%)	15(37%)	71(28%)	0.52
Chronic pulmonary disease	83(32%)	32(31%)	8(19%)	85(34%)	0.67
Chronic kidney disease	38(15%)	18(17%)	8(19%)	34(14%)	0.77
Hypertension	155(59%)	64(61%)	27(66%)	151(61%)	0.74
New York Heart Association class					
I	9(39%)	3(37%)	1(20%)	19(43%)	0.25
II	5(22%)	2(25%)	0(0%)	14(32%)	
III	7(30%)	3(37%)	4(80%)	11(25%)	
IV	2(9%)	0(0%)	0(0%)	0(0%)	
Charlson Comorbidity Index	2.4 ± 2	3.0 ± 2.6	2.8 ± 2.5	2.7 ± 2.3	0.14
ICD implantation	67(25.7%)	28(26.9%)	9(22%)	101(40.6%)	<0.001

SCA = Sudden cardiac arrest; VT = ventricular tachycardia; VF = ventricular fibrillation; PEA = Pulseless electrical activity; BMI = Body mass index; SBP = systolic blood pressure; DPB = diastolic blood pressure; CK-MB = Creatine Kinase- Muscle/Brain isoenzyme; LVEF = Left ventricular ejection fraction; PVD = Peripheral vascular disease; CVD = Cerebrovascular disease; NYHA = New York Heart Association; CCI = Charlson comorbidity index; ICD = Implantable cardioverter defibrillator.

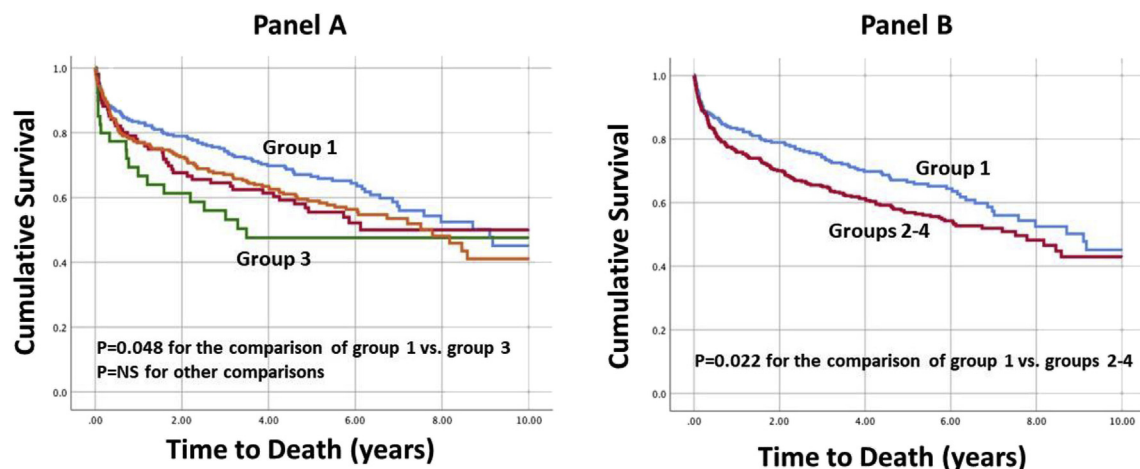


Fig. 2. Kaplan Meier Survival curves for patients by LVEF group (Fig. 2A) and comparing patients with normal LVEF to those with any abnormal LVEF at any time (Fig. 2B).

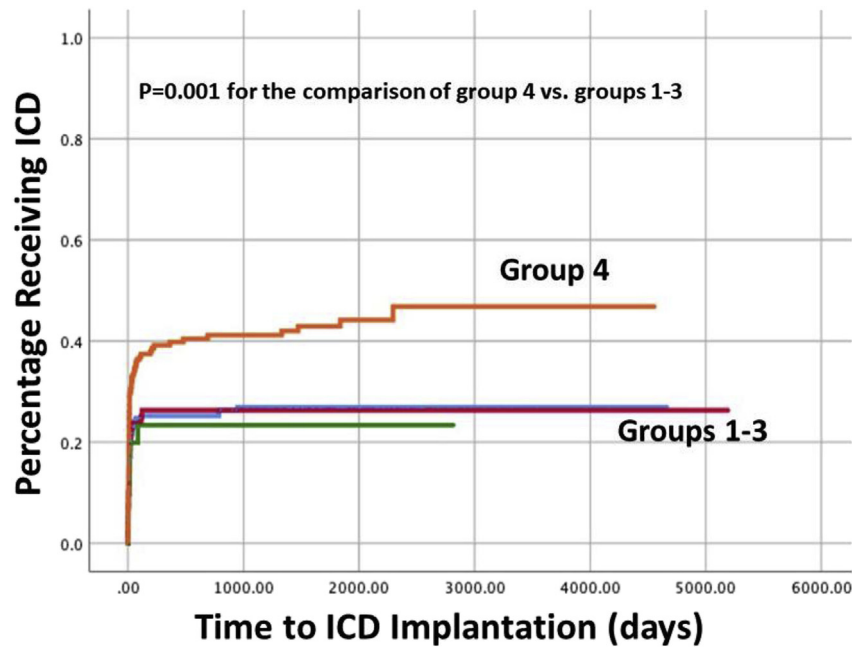
and in follow-up were more likely to live longer whereas patients with reduced LVEF at baseline and in follow-up were more likely to receive ICD therapy. Our data suggest that a preserved LVEF after

SCA is an important predictor of survival even after accounting for ICD therapy. Conversely, ICD therapy was also associated with better survival after accounting for LVEF changes after SCA. Taken

Table 2

Results of multivariable analysis using cox proportional hazard model.

RISK FACTORS	Adjusted hazard ratio (95.0% Confidence Interval)	P-value
BMI (per 1 kg/m ² increase)	1.00 (0.98–1.02)	0.93
QRS duration (per 1 ms increase)	1.00 (0.99–1.01)	0.30
QTc (per 1 ms increase)	1.00 (0.99–1.01)	0.39
Myocardial infarction or ischemia	0.52 (0.39–0.72)	< 0.001
Serum bicarbonate (per 1 mmol/L increase)	1.01 (0.98–1.04)	0.39
Implantable cardioverter defibrillator	0.45 (0.32–0.65)	< 0.001
Any abnormal left ventricular ejection fraction	1.44 (1.05–1.95)	0.02

**Fig. 3.** Time to ICD implantation in SCA survivors, by LVEF group.

together, these findings indicate that prescribing ICD therapy after SCA should not be primarily determined by assessment of myocardial function for secondary prevention of sudden cardiac death.

Classifying SCA survivors by patterns of change in LVEF is a challenging task. We had initially considered using an arbitrary cutoff for the change in LVEF (e.g. 10%) to classify patients into those with improved, stable, or worsening cardiomyopathy. This however had a major short-coming of classifying in the same group very different patients. For a patient with increased LVEF from 10% to 20% is very different from a patient with improved LVEF from 45% to 55%. Similarly, although having similar degrees of cardiomyopathy in follow-up, a patient whose LVEF improves from 25% to 35% may be very different from another whose LVEF worsens from 45% to 35%. Because of all these considerations and in an effort to avoid data fragmentation, we have adopted the approach of classifying patients based on their baseline and follow-up LVEFs, each simply categorized as normal or abnormal.

Transient global myocardial dysfunction after aborted SCA has been well described in literature, classically called post-arrest myocardial dysfunction [4–6,8–10]. The long-term prognosis of patients who have myocardial dysfunction versus preserved cardiac function post aborted SCA is not well known. A recent study by Jentzer et al. [9] investigated early changes in echocardiographic left ventricular systolic and diastolic function in out-of-hospital SCA survivors and its association with mortality using data from

serial transthoracic echocardiography performed at an interval of about 6 days. This study demonstrated a significant improvement in systolic function in all SCA survivors, particularly in those with better long-term prognosis suggesting that changes in LVEF are more predictive of long-term outcomes than immediate post arrest myocardial function [11]. Our present data supports this finding since, in our population, the worst prognosis was seen in patients with initial preserved LVEF who had a decline in their myocardial function in follow-up (group 3). Importantly, our study had a significantly larger number of patients (655 patients versus 59 patients) and a longer time difference between the baseline and follow-up echocardiograms but a comparable follow-up period.

The landmark secondary prevention Antiarrhythmics Versus Implantable Defibrillator (AVID) trial [12], which randomized survivors of SCA to receiving versus not receiving defibrillator therapy demonstrated better long-term survival with the ICD, but this trial only included patients with LVEF $\leq 40\%$. It is therefore unclear whether ICD therapy benefits those survivors who have a normal LVEF after SCA. Our data reflect the findings of AVID since patients with persistently reduced LVEF (group 4) were more likely to be implanted with a defibrillator and this may have been driven by the results of AVID being reflected in daily clinical practice. Although retrospective and observational, our data suggest, in addition, better survival in ICD recipients even after adjusting for LVEF pattern which implies, although do not prove, that patients should be considered for ICD therapy after SCA even if their LVEF is normal.

Our study has limitations. First, it is a retrospective analysis with possible bias. One important such bias is the survival bias whereby only patients who survived long enough to receive a second echocardiographic examination of their LVEF were included in this study. We have, however, minimized referral bias by including all patients who survived a SCA event at our institution without any exclusion criteria. Similarly, we have attempted to reduce other biases by applying appropriate statistical adjustments for between group analyses, thus adjusting for all unbalanced covariates. Second, our study is a single-center analysis, so our results may not be extrapolated to other clinical settings. It is, however, important to note that our institution comprises 25 hospitals spanning western Pennsylvania with clinical settings ranging from small community to larger urban quaternary hospitals. Third, in this analysis we are unfortunately not able to determine the cause of death in long-term follow-up. Lastly, we cannot ascertain if the clinical decision to implant or not implant an ICD implantation was influenced by the initial or follow-up LVEF or whether it was based on other clinical parameters or on the wishes and preferences of patients and their families.

4. Conclusion

In conclusion, we present a large cohort of survivors of SCA who had baseline and follow-up LVEF assessment after the index event. We demonstrate that although ICD therapy is associated with a reduced LVEF at baseline and in follow-up, long-term survival is still highest in patients with normal myocardial function at baseline and in follow-up. We also demonstrate that the worst survival was in the group of patients with declining LVEF overtime. These data have important implications to clinical practice. Importantly, our study

suggests that LVEF patterns after SCA have marginal implications as to who may benefit from ICD therapy after SCA suggesting that ICD therapy should be considered in survivors of SCA regardless of LVEF, a radically different approach compared to ICD indications for the primary prevention of sudden cardiac death.

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