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Ventricular Arrhythmia-Free Survival Following Therapeutic Hypothermia in Patients with Sudden Cardiac Death Due to Ventricular Tachycardia or Fibrillation

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Abstract

Background: The potential benefits of implantable cardioverter-defibrillator (ICD) therapy in patients with sudden cardiac death (SCD) treated with therapeutic hypothermia (TH) have not been well studied. **Methods:** Incidence of recurrent non-sustained ventricular arrhythmia, ICD therapy, and death were ascertained in 64 consecutive survivors of SCD due to ventricular fibrillation or tachycardia, who were treated with TH. Follow-up was 31.5 +/− 3.3 months in 41 ICD recipients and 36.3 +/− 3.9 months in 23 patients who did not receive an ICD due to the presence of a reversible cause of cardiac arrest, an acute myocardial infarction in 87%. **Results:** Combined incidence of ventricular arrhythmia, ICD therapy, or death in patients who underwent ICD placement (21.9%) were similar to overall mortality in the patients who did not receive an ICD (21.7%, $p = 0.752$). ICD placement was associated with a significant mortality benefit; 95.1% survival in ICD recipients vs. 78.3% in the no-ICD group ($p = 0.038$). Electrocardiographic findings of ST segment elevation on admission were associated with increased event rate in ICD recipients ($p = 0.039$) and increased mortality in SCD patients who did not receive an ICD ($p < 0.001$). Other studied variables had no significant effect on the investigated outcomes. **Conclusions:** SCD survivors treated with TH are at increased risk for recurrent arrhythmic events and derive significant mortality benefit from ICD implantation. Increased mortality in revascularized SCD patients with acute coronary syndrome, thought to have a reversible cause of cardiac arrest, calls for prospective trials investigating utility of ICD in this vulnerable patient population.

Keywords

Sudden Cardiac Death, Therapeutic Hypothermia,
Implantable Cardiac Defibrillator

1. Introduction

Each year there are estimated 325,000 cases of sudden cardiac death (SCD) in the United States [1] and approximately 50 per 100,000 cases world-wide accounting for 15% - 20% of all-cause mortality [2] [3] [4] and for >50% of all coronary heart disease related mortality [1] [5] [6]. Described first in the late 1950s [7] [8] [9], therapeutic hypothermia (TH) in SCD patients has consistently demonstrated a mortality benefit with improved functional status [10]-[17] and has since become the standard of care in patients who experience return of spontaneous circulation [18]. Implantable cardioverter defibrillator (ICD) placement is recommended and performed in SCD survivors with projected life expectancy greater than one year and without a reversible cause for cardiac arrest [19]. However, the landmark secondary SCD prevention ICD trials [20] [21] [22] were performed prior to the advent and widespread utilization of TH and the outcomes associated with ICD implantation in SCD survivors treated with TH have not previously been reported. We investigated the incidence and predictors of recurrent ventricular arrhythmias and mortality, as well as the benefits of ICD placement in SCD survivors treated with TH.

2. Methods

2.1. Patient Population and Study Design

The study cohort consisted of 64 consecutive patients with SCD and the initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) that underwent TH and survived to hospital discharge at a single tertiary care academic medical center between 2008 and 2013. Patients with less than 1 year life expectancy and/or with Do Not Resuscitate (DNR) status were excluded from the study cohort.

All patients were treated according to the previously described TH protocol with a target temperature 32 - 34 degrees C over a period of 24 hours [10]. After TH, all patients received guideline directed medical therapy, as dictated by the medical condition [19]. All studied patients were considered for ICD implantation, which was performed in qualified subjects according to the published guidelines [19]. The study control group consisted of SCD-TH survivors who did not have an ICD implanted due to what was thought to be an acute reversible event leading to SCD [19].

2.2. Data Collection

The presence of ST segment elevation (STE) on the first recorded electrocardio-

gram (ECG) after defibrillation was ascertained according to the Third Universal Definition of Myocardial Infarction criteria, as at least 0.1 mV STE 60 - 80 msec after the J point, in two contiguous leads other than V1 and V2 [23]. In patients who underwent coronary angiography, presence of significant obstructive atherosclerotic coronary artery disease (CAD) was defined as one or more epicardial coronary arteries with stenosis of greater or equal to 50% in left main coronary artery or 70% in the left anterior descending, circumflex, or right coronary arteries [24].

Echocardiograms at the time of the index SCD event and at 3 month follow-up were acquired according to the American Society of Echocardiography recommendations [25]. LV systolic function was graded as preserved if EF was greater or equal to 55%. LV systolic dysfunction was graded as mildly reduced if EF was 45% - 54%, moderately reduced if EF was 30% - 44%, and severely reduced if EF was <30% [25].

For patients who had ICDs implanted, frequency and timing of shock (high voltage therapy with defibrillation) or anti-tachycardia pacing (ATP) were determined from serial ICD transmissions and device interrogations. All tracings were reviewed manually by the Board certified electrophysiologists to exclude episodes of inappropriate shock or ATP for atrial arrhythmias, electrical magnetic interference, myopotentials, lack of lead integrity, and therapy for oversensing.

Two studied endpoints included all-cause mortality and a composite endpoint of mortality and appropriate device therapy (ATP or high voltage therapy with defibrillation) in ICD recipients and, since the arrhythmic events could not be ascertained in SCD-TH survivors who did not have an ICD implanted, mortality alone in the no ICD group. Event rates were compared between SCD-TH survivors who did and did not have an ICD implanted.

Overall mortality and device therapy and arrhythmia-free mortality were assessed at 1-year post discharge and at the end of the follow-up period. Mortality was determined through the medical charts, including the outpatient office follow-up records, and ascertained through the National Death Index. Cause of death was obtained from death certificates and discharge summaries.

This was a retrospective cohort study, which involved no risk for the subjects, with the waiver of informed consent not adversely affecting the rights and welfare of the subjects. The study was approved by the Institutional Review Board.

2.3. Statistical Analysis

Continuous data was expressed as means with standard deviations. Differences in continuous variables were assessed with an unpaired t-test and non-parametric Kruskall-Wallis test, when appropriate. Categorical data was expressed as proportions and the differences in proportions were assessed with Fisher's exact test. Mortality and time to device therapy were analyzed using Kaplan-Meier estimates with Mantel-Cox log-rank test for between group differences.

Variables associated with mortality, defibrillation, or ATP were further sub-

jected to logistic regression analysis. Variables found to be associated with mortality or device therapy in a univariable logistic regression were then retained in the multivariable logistic regression analysis.

In all analyses, p-value ≤ 0.05 was defined as statistically significant. Based on the previously reported 25% rate of recurrent arrhythmic or death rate in SCD patients (20 - 22) and the Type I error probability of 0.05, the study consisting of 41 ICD recipients and 23 control patients had power of 0.348 to detect a 25% absolute difference in outcomes and power of 0.958 to detect a 50% absolute difference. Analysis was performed using commercially available statistical software (SAS Institute Inc., Cary, NC, 2007).

3. Results

The study cohort consisted of 64 consecutive SCD patients with cardiac arrest due to ventricular tachycardia or fibrillation, who were treated with therapeutic hypothermia and survived to hospital discharge. Median follow-up length was 31.5 +/− 3.3 months in the ICD group and 36.3 +/− 3.9 months in the no-ICD group. Of the 23 patients in the no-ICD arm, an ICD was not implanted in 2 patients with hyperkalemia and in 1 patient with prolonged QT on presentation, which re-solved with correction of electrolytes and outpatient drug discontinuation respectively. An ICD was also not implanted in an additional 20 patients who were presumed to have an acute ischemic event leading to SCD and did not meet MUSTT criteria [26].

Coronary angiography was performed in 59 patients, and 43 were found to have obstructive CAD which required revascularization in 67.4% (29/43). Of 10 patients who underwent coronary artery bypass grafting, 5 received ICD (50%); of 19 patients who underwent percutaneous coronary intervention, 8 received an ICD (42%, $p = 0.241$). Patients with obstructive CAD or ST elevations were significantly less likely to receive an ICD (54.5% vs. 85% in patients without ST elevation or obstructive CAD, $p = 0.019$). Otherwise, there were no significant differences, including initial or follow-up evaluation of systolic function as evidenced by the LV ejection fraction (EF), between the patients who did or did not receive an ICD (**Table 1**). Ten patients presented with ST elevation and all were subsequently found to have obstructive coronary disease. Obstructive coronary artery disease was also found in 33 of 49 patients who presented without ST elevation.

A total of 7 patients expired during the follow-up period, 2 with and 5 without ICD implantation. Of those without an ICD, four patients died of cardiac arrest; other causes of death were intracranial hemorrhage, pneumonia, and congestive heart failure. Of the 2 expired patients with ICD implantation, one died from cardiopulmonary arrest and the other from heart failure.

During the specified follow-up period, appropriate ICD therapy occurred in 7 patients (**Table 1**). Non-sustained ventricular tachycardia (NSVT) which did not require device therapy was noted in 2 additional patients. None of the baseline parameters, distinguished SCD-TH survivors who required appropriate device

Table 1. Factors associated with ICD implantation and subsequent device therapy.

Category	No-ICD vs. ICD Comparison			ICD Rx vs. ICD No-Rx and vs. No-ICD Comparison			
	No-ICD N = 23	ICD N = 41	*p*-value	No-Rx N = 34	Rx N = 7	Rx vs. No-Rx p-value	No-ICD vs. Rx vs. No-Rx p-value
Age (years old)	60 (15.3)	58.1 (13.4)	0.625	57.6 (12.7)	61 (17.6)	0.544	0.582
Weight (kg)	81 (15.5)	87.0 (23.3)	0.276	89.7 (24.1)	74.0 (13.1)	0.105	0.172
Gender, Females	3 (13)	9 (22)	0.767	6 (17.6)	3 (42.9)	0.142	0.203
Systolic BP (mmHg)	117 (43.5)	126.6 (29.7)	0.303	125.4 (28.6)	132.1 (36.2)	0.592	0.387
Heart Rate (bpm)	87.3 (26.8)	85.3 (16.6)	0.709	85.1 (17.6)	86.0 (11.5)	0.899	0.943
Ejection Fraction							
<35%	6 (26.1)	16 (39)		13 (38.2)	3 (42.9)		
35% - 39%	4 (17.4)	7 (17.1)	0.729	4 (11.8)	3 (42.9)	0.282	0.537
40% - 54%	1 (4.3)	2 (4.9)		2 (5.9)	0		
>54%	12 (52.1)	16 (39)		15 (44.1)	1 (14.3)		
ST Elevation	7 (30.4)	4 (9.8)	0.035	4 (11.8)	0 (0)	0.339	0.083
K (mg/dL)	3.6 (0.7)	4 .1(1.1)	0.113	3.9 (1.0)	4.4 (1.7)	0.374	0.254
Creatinine (mg/dL)	1.6 (1.1)	1.9 (2.3)	0.453	1.8 (1.9)	2.7 (3.8)	0.364	0.842
pH (units)	7.27 (0.148)	7.244 (0.124)	0.465	7.234 (0.133)	7.291 (.045)	0.272	0.397
Glucose (mg/dL)	195.4 (53.8)	227.3 (115.0)	0.225	228.2 (112.2)	223.0 (137.5)	0.915	0.630
Ca (mg/dL)	8.2 (0.8)	8.2 (0.70)	0.794	8.2 (0.7)	8.1 (0.7)	0.626	0.840
Mg (mg/dL)	1.9 (0.30)	2 .0 (0.4)	0.519	2 (0.4)	1.9 (0.2)	0.453	0.567
Hemoglobin (mg/dL)	13.5 (1.8)	13.5(1.9)	0.929	13.5 (1.9)	13.8 (2.2)	0.688	0.940
Hematocrit (units)	40.3 (5)	39.8 (5.7)	0.745	39.7 (5.7)	40.4 (6.5)	0.786	0.950
Obstructive CAD	20/21 (95.2%)	23/38 (60.5%)	0.004	19/31 (61.3%)	4/7 (57.1%)	0.839	0.016
Alive at 1 year	20 (86.9%)	39 (95.1%)	0.243	32 (94.1%)	7 (100%)	0.511	0.439
Alive at 2.5 years	18 (78.3%)	39 (95.1%)	0.038	32 (94.1%)	7 (100%)	0.511	0.105

Numbers represent means (SD) or absolute counts (%).

therapy after the hospital discharge (Table 1) from those patients who did not, including reduced EF ($p = 0.282$) or significant obstructive coronary artery disease ($p = 0.839$).

All recorded follow-up deaths occurred within 24 months from the index event hospitalization (Figure 1). ICD placement was associated with a trend towards improved 1 year survival, which was found to be significant at the end of 2.5 year follow-up ($p = 0.038$, Table 2, and log-rank $p = 0.05$, Figure 1(a)). Advanced age ($p = 0.044$) and ST elevation on admission ($p < 0.001$) were associated with decreased survival (Table 2). In multivariable logistic regression analysis including age, ejection fraction < 35%, and ICD status, only ST elevation on admission for cardiac arrest was associated with decreased survival (Table 3, log-rank $p = 0.011$, Figure 1(b)).

There was no difference in EF between patients who presented with ST eleva-

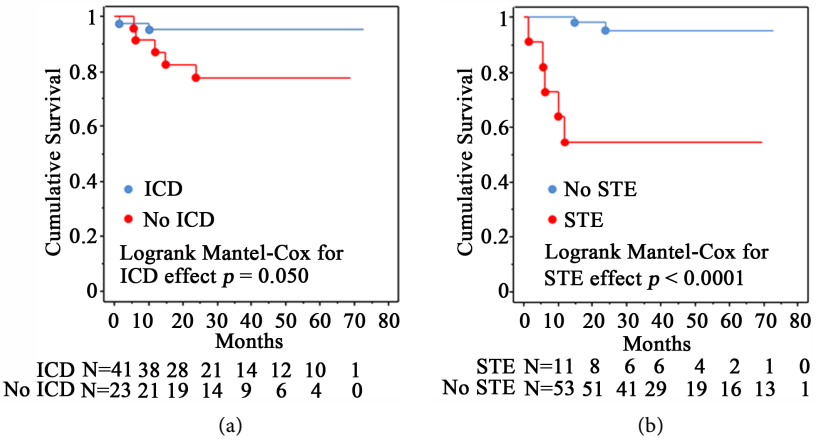

Figure 1. Kaplan Meier survival estimates. (a) Long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ICD status; (b) Long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ST elevation on admission. ICD placement was associated with improved long-term survival. Admission ST elevation (STE) was associated with decreased long-term survival.

Table 2. Factors affecting follow-up survival.

Category	1 year follow up			End of study (2.5 year) follow up		
	Alive N = 59	Expired N = 5	*P*-value	Alive N = 57	Expired N = 7	*P*-value
Age (years old)	57.9 (14.0)	68.8 (11.1)	0.0974	57.6 (13.7)	68.9 (13.4)	0.044
Weight (kg)	85.6 (21.3)	76.0 (14.2)	0.324	86.5 (21.1)	71.7 (13.9)	0.077
Gender, Females	12 (20.3)	0 (0)	0.263	12 (21.1)	0(0)	0.178
Systolic BP (mmHg)	122.8 (35.3)	128.6 (35.1)	0.724	123.0 (36.0)	125.1 (29.3)	0.879
Heart Rate (bpm)	85.8 (19.0)	87.8 (37.8)	0.839	85.7 (18.9)	88.1 (33.1)	0.771
Ejection Fraction						
<35%	20 (33.9)	2 (40)		20 (35.1)	2 (28.6)	
35% - 39%	11 (18.6)	0	0.197	11 (19.3)	0	0.287
40% - 54%	2 (3.4)	1 (20)		2 (3.5)	1 (14.3)	
>54%	26 (44.1)	2 (40)		24 (42.1)	4 (57.1)	
ST Elevation	6 (10.2)	5 (100)	0.0001	6 (10.5)	5 (71.4)	0.0001
K (mg/dL)	3.9 (1.9)	3.9 (0.3)	0.925	3.9 (1.1)	3.8 (0.4)	0.873
Creatinine (mg/dL)	1.8 (2.1)	1.5 (0.4)	0.686	1.8 (2.1)	2 (1.4)	0.806
pH (units)	7.255 (0.131)	7.235 (0.160)	0.777	7.246 (0.123)	7.318 (0.201)	0.206
Glucose (mg/dL)	219.6 (101.2)	176.6 (55.3)	0.355	221.9 (102.1)	169.9 (48.8)	0.19
Ca (mg/dL)	8.2 (0.7)	8.5 (0.3)	0.451	8.2 (0.7)	8.4 (1.1)	0.45
Mg (mg/dL)	2 (0.3)	2.1 (0,2)	0.468	2 (0.4)	2.1 (0.2)	0.513
Hemoglobin (mg/dL)	13.6 (1.9)	12.7 (1.4)	0.302	13.7 (1.9)	12.4 (1.3)	0.101
Hematocrit (units)	40.1 (5.6)	38.6 (4.6)	0.0558	40.3 (5.6)	37.9(4.0)	0.284
Obstructive CAD	39/55 (70.9%)	4/4 (100%)	0.206	39/54 (72.2%)	4/5 (80%)	0.708
ICD	39/59 (66.1%)	2/5 (40)	0.243	39/57 (68.4%)	2/7 (28.6%)	0.038

Numbers represent means (SD) or absolute counts (%).

Table 3. Logistic regression analysis of the survival predictors.

Category	Univariable analysis			Multivariable analysis		
	Exp (Coef)	95% Confidence Intervals	*p*-value	Exp (Coef)	95% Confidence Intervals	*p*-value
Age (Per Year)	0.928	0.862 - 0.999	0.048	0.934	0.858 - 1.016	0.112
EF < 35%	0.740	0.131 - 4.165	0.733	0.462	0.031 - 6.954	0.577
ST Elevation	0.047	0.007 - 0.298	0.001	0.053	0.005 - 0.516	0.011
ICD	5.417	0.958 - 30.630	0.056	1.874	0.154 - 22.803	0.622

tions vs. those without ST segment elevation (p = 0.485). Likewise, a reduced LVEF was not predictive of decreased survival (Table 2). Of the expired ICD recipients, one had an LVEF of 40% - 49% and another one had an LVEF < 35%. Of the 5 expired patients in the no-ICD group, 4 had an LVEF > 50%, and only one patient had an LVEF of < 35%, a non-significant difference (p = 0.287, when compared to ICD group).

Incidence of arrhythmic event or death, an arrhythmia-free survival, in ICD group was compared to all-cause mortality in patients who did not receive an ICD (Figure 2). There were a total of 9 events (21.9%) in the ICD group and 5 events (21.7%) in the no-ICD group, a non-significant difference (log-rank p = 0.752, Figure 2(a)). In both the ICD and no-ICD groups, ST elevation on admission was associated with decreased arrhythmia-free survival (log-rank p = 0.039, Figure 2(b)).

4. Discussion

Therapeutic hypothermia (TH) has consistently demonstrated a mortality benefit with improved functional status [10]-[17] and it is widely implemented in SCD patients who experience return of spontaneous circulation [18]. We have conducted a retrospective cohort study of patients with SCD due to ventricular fibrillation or tachycardia, who were treated with TH (VT-VF SCD-TH) and subsequently underwent an ICD placement according to the current standard of care based on the landmark secondary SCD prevention ICD trials, the Cardiac Arrest Study Hamburg (CASH) [21], the Canadian Implantable Defibrillator Study (CIDS) [22], and The Antiarrhythmics versus Implantable Defibrillators (AVID) trials [20]. However, these landmark secondary SCD were performed prior to the advent and widespread utilization of TH, and the outcomes associated with ICD implantation in SCD survivors treated with TH have not previously been reported.

In the studied contemporary cohort of VT-VF SCD-TH patients, ICD placement was associated with a significant improvement in overall survival, while those discharged without an ICD remained at high mortality risk. Reduced LV ejection fraction had no effect on outcomes, mean-while ST segment elevation or obstructive CAD portended a poor prognosis.

The mortality rate of VT-VF SCD-TH survivors was 10.9%, which is better than reported 24% mortality during 2 year follow-up in AVID [20], 21% during

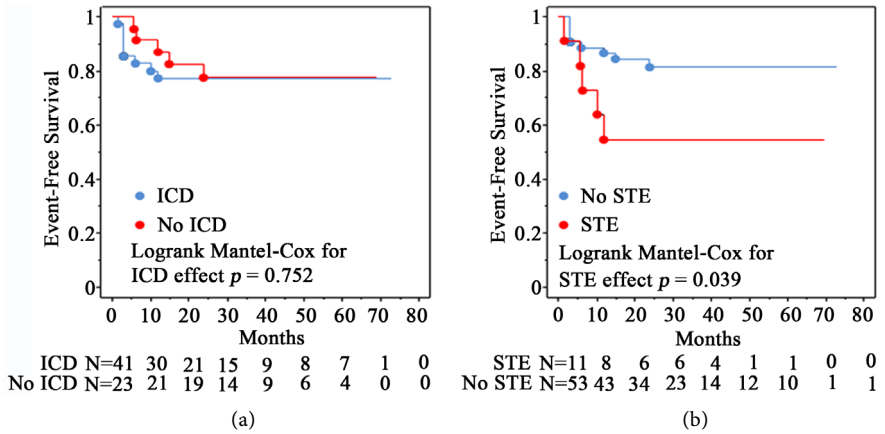

Figure 2. Kaplan Meier time to death or ICD therapy estimates. (a) Arrhythmia-free long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ICD status; (b) Arrhythmia-free long-term survival in SCD patients treated with therapeutic hypothermia, stratified by ST elevation on admission. ICD placement did not affect long-term ICD therapy-free survival. Admission ST elevation (STE) was associated with decreased ICD therapy-free survival.

2 year follow up in CIDS [22], and the 44% rate over 5 years in CASH trials [21]. It is possible that improved survival in VT-VF SCD-TH patients is reflective of the TH benefits [10] [11]. Also, the decreased mortality may be due to consistent utilization of the evidence based modern optimal medical therapy (OMT) in patients with ASCVD, which included beta-adrenergic blockers and angiotensin-converting enzyme inhibitors in all qualifying subjects, which was not used consistently in prior studies [20] [21] [22].

The observed rates of ICD therapy in VT-VF SCD-TH cohort were 14.6% during the first year, and a total of 17.0% by the end of the 2.5 year study follow-up period, an annual device therapy rate of 6.9%. The observed annual device therapy rate in VT-VF SCD-TH patients is comparable to 5% annual event rates reported in primary SCD prevention trials including SCD-HeFT [27] and MADIT II [28]. The device therapy rates were not reported in CASH, CIDS, and AVID trials [20] [21] [22].

A substantial number of VT-VF SCD-TH survivors, 23 of 64 patients in our study, did not undergo ICD implantation due to suspected reversible causes of cardiac arrest. All patients in our study were evaluated prior to discharge for ICD implantation, and neurologic status was specifically addressed; patients with poor neurologic status, DNR/DNI status, and patients with limited life expectancy of <1 year were excluded from the study. The remaining 64 patients included in the study did not have significant neurologic deficits following TH. In our study, the observed annual mortality rate in VT-VF SCD-TH survivors who did not receive an ICD was 8.7%, with more than half of the deaths attributed to cardiac arrest. This mortality rate is comparable to the annual mortality rates noted in the landmark primary SCD prevention trials: 7.2% rate in SCD-HeFT control group [27] and 8.0% rate in MADIT II control group [28]. Our findings suggest that regardless of the ICD allocation, VT-VF SCD-TH patients have sig-

nificantly increased mortality risk, which is mostly due to arrhythmic events, consistent with data from the landmark secondary and primary SCD prevention trials.

Historically, reduced LV systolic function has predicted increased mortality and has been associated with primary prevention benefit in ICD recipients [20] [21] [22]. Effects of LV function on incidence of arrhythmic events/deaths in VT-VF SCD-TH survivors have not previously been well studied. In our investigation, 83.3% of VT-VF SCD-TH treated patients who required ICD therapy had an EF > 35% at the time of the 3 month follow-up evaluation, and only one expired patient had EF < 35%. Of the 10 patients with decreased ejection fraction, who did not attain an ICD prior to discharge, nine presented with ST elevations and one with hyperkalemia which were thought to be the reversible causes of SCD. In all 10 patients subsequent echocardiograms demonstrated LV ejection fraction improvement to >40% at 3 - 6month follow up intervals. Thus, while surprising, our results indicate that left ventricular systolic dysfunction alone may not be a significant determinant of mortality or future device therapy in VT-VF SCD-TH patients, possibly due to better myocardial salvage and cardio-protective effects of TH noted in the experimental studies [29]. It is possible that patients with significant pre-arrest LV systolic dysfunction were less likely to survive the index event, which has resulted in selection bias towards patients with preserved ejection fraction, thus explaining limited significance of LV dysfunction in predicting cardiac events during follow-up. However, this "selection bias" is not unique to our patients, but is a common attribute in all survivors of sudden cardiac death.

In our study, the evidence of ischemia, defined by ST elevation or significant obstructive CAD, was predictive of adverse outcomes in VT-VF SCD-TH patients, adding to the body of evidence linking ventricular arrhythmias, acute ischemic events, and increased mortality in SCD patients. Ischemia may trigger ventricular tachycardia and, reciprocally, decreased coronary perfusion due to ventricular arrhythmia may progress to transmural ischemia in patients with obstructive coronary artery disease [24] [30]. In fact, late gadolinium enhancement pattern consistent with unidentified prior myocardial infarction has been demonstrated in 58% of SCD survivors with unclear etiology of cardiac arrest [31].

SCD risk stratification strategy in patients with an acute ischemic event is evolving. ICD benefit has been demonstrated in primary SCD prevention trials in patients with acute myocardial infarction and depressed ejection fraction < 35% [32] or when LV ejection fraction < 40% was ac-companied by non-sustained ventricular tachycardia and an inducible sustained ventricular tachycardia at the electrophysiologic study [26]. ICD implantation has been associated with improved survival in patients with ejection fraction > 35% who suffered SCD from an ischemic event [33]. However, since acute myocardial ischemia may be a reversible cause of cardiac arrest, SCD treated patients with obstructive CAD or ST elevations are currently not considered for secondary prevention and do

not undergo ICD implantation [19].

In studied SCD survivors treated with therapeutic hypothermia, the mortality rate in patients who did not qualify for ICD placement was similar to a combined device therapy and mortality rate in ICD recipients. This suggests that VT-VF SCD-TH survivors with an ischemic substrate may be at increased risk of recurrent arrhythmic events, despite preserved left ventricular systolic function and improved hospital survival, which is likely associated with benefits of TH [10] [11]. Foregoing ICD implantation in these patients, based on assumption that there was a reversible cause of SCD, may leave them potentially unprotected against future SCD events. The DINAMIT trial of patients after an acute coronary event found that early implantation of ICD was associated with decrease in SCD but no overall mortality benefit [32]. Our study population is very different from DINAMIT in that all of our patients have presented with SCD and were treated with TH; a population that was not represented in significant numbers in the DINAMIT study [32]. The population of SCD-TH survivors regardless of etiology is as yet an unstudied population with respect to randomized clinical trials. Our study indicates that there may be potential mortality benefit in early ICD implantation in survivors of SCD due to ventricular tachycardia or fibrillation, treated with TH; however, this statement of course will require a randomized clinical trial for confirmation.

5. Limitations

We consider our findings to be hypothesis generating and requiring confirmation in prospective trials. This was a single site retrospective study involving a modest number of subjects with an inherent selection bias for patients who are most likely to survive a cardiac arrest due to ventricular fibrillation or tachycardia. Patients who did not survive to hospital admission or passed away during hospitalization represent a different sample of patients; however, because the goal of this trial was to provide insight into the potential role of ICD in VT-VF SCD-TH survivors, looking at only candidates for ICD implantation gives the real world experience, according to the accepted practice patterns. Patients were not randomized to treatment categories; instead, everyone was treated according to the established guidelines, once again, making our findings clinically relevant. Lastly, patients who did not receive an ICD were not prospectively monitored for incidence of arrhythmia; instead, causes of death were ascertained from death certificates and discharge summaries and could not be independently adjudicated. Future studies of similar nature may be conducted with implantable or wearable cardiac telemetry recorders in VT-VF SCD-TH patients who currently do not qualify for ICD placement.

6. Conclusion

To our knowledge, this is the first study specifically investigating outcomes in survivors of sudden cardiac death due to ventricular tachycardia or fibrillation treated with therapeutic hypothermia. We have observed that these SCD patients

are at increased risk of recurrent arrhythmia and derive benefit from ICD implantation comparable to such reported in the landmark secondary SCD prevention trials, which were performed prior to the advent of therapeutic hypothermia. In this patient population, a preserved systolic function does not appear to confer a follow-up survival benefit; however, obstructive coronary artery disease and ST segment elevation at the time of presentation are associated with an increased mortality during a 2.5 year follow-up period. Therefore, the VT-VF SCD-TH survivors with an ischemic substrate appear to be at increased risk of death, likely due to recurrent arrhythmias, and, without an ICD implantation, may be potentially unprotected against future SCD events. Our findings need to be confirmed in a prospective randomized trial designed to evaluate the mortality benefit of ICD implantation after therapeutic hypothermia, including patients with the presumed ischemic etiology of an arrhythmic event. Until further studies, close monitoring for recurrent arrhythmias is imperative in this vulnerable patient population.

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