

Ischemic Heart Disease Diagnosed Before Sudden Cardiac Arrest Is Independently Associated With Improved Survival

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Background—Sudden cardiac arrest (SCA) is a significant public health problem, and rates of survival after resuscitation remain well below 10%. While several resuscitation-related factors are consistently associated with survival from SCA, the impact of specific comorbid conditions has not been assessed.

Methods and Results—The Oregon Sudden Unexpected Study is an ongoing, multisource, community-based study in Portland, Oregon. Patients with SCA who underwent attempted resuscitation between 2002 and 2012 were included in this analysis if there were both arrest and prearrest medical records available. Information from the emergency medical services system, medical examiner, public health division, hospitals, and clinics was used to adjudicate SCA, evaluate comorbidities, and identify medical treatments. Univariate and multivariate analyses were performed to investigate the influence of prearrest comorbidities on survival to hospital discharge. Among 1466 included patients, established resuscitation-related predictors (Utstein factors) were associated with survival, consistent with prior reports. When a panel of prearrest comorbidities was evaluated along with Utstein factors, recognized coronary artery disease was significantly associated and predicted *higher* odds of survival (unadjusted odds ratio 1.5, $P<0.001$; adjusted odds ratio 1.5, $P=0.02$). In multivariable logistic models, prearrest coronary artery disease modified the survival effects of bystander cardiopulmonary resuscitation, but did not modify other Utstein factors.

Conclusions—An established diagnosis of coronary artery disease was associated with 50% higher odds of survival from resuscitated SCA after adjustment for all arrest-related predictors. These findings raise novel potential mechanistic insights into survival after SCA, while highlighting the importance of early recognition and treatment of coronary artery disease. (*J Am Heart Assoc.* 2014;3:e001160 doi: 10.1161/JAHA.114.001160)

Key Words: atherosclerosis • heart arrest • myocardial infarction • sudden death

Sudden cardiac arrest (SCA) is responsible for half of cardiovascular deaths and a greater burden of premature death than any individual disease.¹ Survival after cardiac arrest is dependent on several prehospital resuscitation factors. These “Utstein” data elements² are tracked by emergency medical services (EMS) systems around the world for SCA and other categories of out-of-hospital cardiac arrest.

The Utstein elements serve important purposes including prognostication in the early postarrest phase, comparison of risk-adjusted outcomes between emergency response systems, and evaluation of the risk-adjusted impact of new interventions. Several core Utstein elements are well-established predictors of survival: presumed cardiac etiology, witnessed status, location of arrest, bystander cardiopulmonary resuscitation (CPR), attempted defibrillation, and initial presenting rhythm. Nonetheless, these Utstein resuscitation factors account for only 72% of survival variability between EMS sites for overall arrests and only 40% of survival variability for the subset of bystander-witnessed SCA from presumed cardiac cause.³ Likely due to logistical difficulties, intrinsic patient-related factors such as preexisting disease conditions have not been previously evaluated. An improved understanding of the predictors of SCA survival could allow for explanation of heterogeneity in response to cardiac arrest resuscitation, better risk-adjustment for outcomes, and identification of novel strategies for improvements in resuscitation.

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Methods

Study Population and Adjudication of SCA

Patients from the Oregon Sudden Unexpected Death Study (SUDS) with SCA and attempted resuscitation between 2002 and 2012 were included in the present study if >18 years old. Oregon SUDS is a community-based study in the Portland metropolitan area (population 1 million) that uses multisource case ascertainment of SCA. It was approved by the institutional review boards of all local hospitals, and all living patients gave informed consent for participation. In the complete ascertainment period of this Oregon SUDS resuscitation study (first 3 years), all SCA cases from 1 county were actively recruited through intensive and frequent interactions with the local EMS system. Subsequently, patients undergoing resuscitation were recruited from the overall metropolitan area, although not all individual EMS crews opted to enroll patients. Information was obtained from the EMS system, state public health division, medical examiner, and local hospitals and clinics. In aggregate, these records provided information describing the patients' medical status before SCA arrest, as well as the arrest circumstances (including bystander comments and rhythm tracings) and prehospital care. Posthospital care information such as physician diagnosis at the time of discharge/death and treatment with coronary angiography was also incorporated when applicable. A 2-stage adjudication process was used, requiring the consensus opinion of 3 physicians who are expert in SCA definitions. In the first stage, information from the EMS system and any known medical history were used to preliminarily categorize as either possible SCA or definitive non-SCA. After additional information was obtained for possible SCA cases (prearrest medical records, postresuscitation medical records, and any autopsy records), a second-stage adjudication resulted in final categorization.

Data and Definitions

SCA was defined according to standard criteria for both witnessed and unwitnessed cases.⁴ Only patients with attempted resuscitation (with or without hospital transport) and records available for documentation of prearrest health status were included in this analysis. Witnessed SCA cases were those with abrupt loss of pulse after being observed in normal health. Unwitnessed SCA cases were those with circumstances consistent with abrupt loss of pulse in patients seen alive and in normal health within the preceding 24 hours. Witnessed and unwitnessed cases were excluded if there was a likely nonarrhythmic cause of death or known terminal illness. With the exception of survival information, only clinical information obtained before cardiac arrest was

used for this analysis, to reduce the risk of workup bias for cardiac arrest survivors.

Prearrest comorbidities were determined based on documentation of physician diagnosis or diagnostic test results before SCA. Established coronary artery disease (CAD) was defined as chart or cardiovascular imaging documentation of $\geq 50\%$ stenosis of a coronary artery, prior myocardial infarction (MI), or prior revascularization. MI was defined as MI documented in a physician note or cardiovascular imaging test without distinction between ST-segment elevation MI and non-ST-segment elevation MI. Other comorbidities were recorded as present if they were documented in the past medical history or assessment section of a clinician's note. Survival was defined as survival to hospital discharge. Core Utstein data elements, as defined previously,² were abstracted from EMS records.

Prearrest medication use was abstracted from the most recent medical records containing a list of medications. Antiplatelet agents were defined as any medication or combination of medications containing aspirin, ticlopidine, or clopidogrel. β -Blockers were identified as any medication or combination with β_1 - or β_2 -adrenergic receptor antagonism properties, angiotensin-converting enzyme inhibitors as those with angiotensin-converting enzyme inhibition properties, statins as those with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition properties, and antiarrhythmic agents as those with Vaughn Williams class 1 or 3 properties.

Statistical Analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc). Univariate differences in demographic, prearrest, and arrest characteristics were compared using χ^2 and Fisher exact tests for categorical variables and 2-sample *t* tests for continuous variables. Categorical variables were expressed as proportions and continuous variables as a mean \pm SD. Odds ratios (Ors) were expressed along with 95% CIs. In addition to CAD, a panel of major comorbidities was evaluated in univariate testing for any potential association with survival. Multivariable logistic models were created evaluating the prediction of survival by 7 Utstein resuscitation factors (age, sex, witnessed arrest, public location, bystander CPR, presenting arrhythmia, EMS response time), as well as prearrest CAD or MI.

Two secondary analyses were performed to add context to the primary findings. One evaluated the impact of prearrest medication use on survival. Univariate testing of medications for association with survival was performed using logistic modeling. Multivariate testing was performed using 5 models, each containing the 7 Utstein resuscitation factors outlined plus a single medication class. The other secondary analysis evaluated whether the presence of prearrest CAD modified

the effects of the Utstein resuscitation factors on survival. Seven multivariable logistic models of survival were constructed containing the 7 Utstein elements plus prearrest CAD and an interaction term (1 in each model for interaction between prearrest CAD, a single Utstein factor).

Results

Between 2002 and 2012, 1466 patients experienced sudden cardiac arrest with attempted EMS resuscitation and had arrest and prearrest medical records available. The mean age was 65 ± 16 years, with 33% women and an overall survival rate of 15%. Before cardiac arrest, 41% of patients had a history of CAD and 31% had a history of MI. Of patients with prearrest CAD, 58% were treated with antiplatelet agents, 64% with β -blockers, 48% with angiotensin-converting enzyme inhibitors, 56% with statins, and 8% with antiarrhythmic agents.

Influence of Utstein Factors and Prearrest CAD on Survival

All of the Utstein resuscitation factors that have been previously identified as predictors of survival to hospital discharge were also predictive in this study (Table 1). A total of 598 (41%) patients had CAD diagnosed before cardiac arrest. The odds of survival among patients with known CAD were significantly *higher* (OR 1.5; $P=0.007$).

All major comorbidities aside from CAD and MI were present in similar proportions between survivors and nonsurvivors (Table 2). The mean Charlson Comorbidity Index score was nearly identical between groups, as was the proportion of patients with scores ≥ 4 . In multivariable logistic modeling, all Utstein factors except bystander CPR ($P=0.14$) remained statistically significant (Table 3). A history of prearrest CAD or MI independently predicted increased survival with similar

magnitude to univariate analysis. When interaction testing was performed between prearrest CAD and each Utstein data element individually, prearrest CAD modified the survival effect of bystander CPR (P value of interaction term 0.004) but none of the other factors.

Influence of Prearrest Medications on Survival

In a univariate analysis of the 1276 patients with information available on all Utstein factors as well as prearrest medications, the use of antiplatelet agents, β -blockers, angiotensin-converting enzyme inhibitors, and antiarrhythmic agents was not associated with differences in survival. Statin use was associated with improved survival in univariate analysis, with an OR of 1.6 (95% CI 1.1 to 2.2). In multivariable analysis, statins were not predictive after adjustment for Utstein resuscitation factors and prearrest CAD. Prearrest CAD remained statistically significantly associated with survival in all multivariable models.

Discussion

In this community-based study of 1466 patients with SCA and detailed prearrest medical records, the presence of CAD diagnosed before SCA was associated with a greater likelihood of survival after resuscitation. Patients with prearrest CAD had 50% higher odds of survival after adjustment for Utstein resuscitation factors. Major noncardiac comorbidities and Charlson comorbidity scores were not predictive of survival outcome. In unadjusted analysis, prearrest medical therapy with a statin was associated with improved survival; however, this relationship was no longer significant after adjustment for other predictors. Prearrest CAD modified the survival effect of bystander CPR, but there was no interaction between prearrest CAD and the other Utstein factors.

Table 1. Comparison of Utstein Characteristics for Sudden Cardiac Arrest Survivors and Nonsurvivors

Utstein Element	All Subjects (n=1466)	Survivors (n=220)	Nonsurvivors (n=1246)	P Value
Age, y	65 ± 16	61 ± 15	66 ± 16	<0.001
Female	33%	35%	32%	0.41
Witnessed	69%	89%	66%	<0.001
Public location	33%	53%	30%	<0.001
Bystander CPR	30%	43%	28%	<0.001
Initial rhythm VT/VF	49%	87%	42%	<0.001
EMS service response time, min	6.8 ± 3.3	6.4 ± 3.1	6.9 ± 3.3	0.04

Due to missing data, the smaller denominators were used for the following variables: response time (n=1294), arrest location (n=1458), witnessed status (n=1457), and initial rhythm (n=1409). P values are listed for comparisons between survivors and nonsurvivors. CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. Univariate Evaluation of the Influence of Prearrest Comorbidities on Survival

Comorbidity	Odds Ratio (95% CI)	P Value
Coronary artery disease	1.5 (1.1 to 2.0)	0.007
Myocardial infarction	1.6 (1.2 to 2.2)	0.001
Diabetes	0.95 (0.70 to 1.3)	0.75
Cancer (in remission)	1.1 (0.69 to 1.6)	0.77
Chronic obstructive pulmonary disease	0.79 (0.55 to 1.2)	0.21
Chronic kidney disease	0.96 (0.67 to 1.4)	0.83
History of stroke	0.69 (0.44 to 1.1)	0.10
Charlson Comorbidity Index score ≥ 4	1.0 (0.73 to 1.38)	0.96

At this time, any potential explanations for these findings are speculative. It is possible that patients with known CAD may have had greater awareness regarding activation of EMS for ischemic symptoms. This may have resulted in a shorter duration between onset of SCA and onset of EMS resuscitation efforts. Another possibility is that prior ischemia in patients with known CAD may have resulted in a protective “preconditioning” effect,^{5–8} which may be less likely to occur in patients with undiagnosed CAD and a catastrophic event such as a sudden MI that triggered ventricular fibrillation. Both clinical and mechanistic studies have clearly established that reversible periods of cardiac ischemia immediately before acute MI or global ischemia induce metabolic changes that limit infarct size, promote myocardial recovery, and lower rates of lethal arrhythmias.^{5,6,8} A third possibility is that emergency response systems and advanced cardiac life support algorithms have been developed in a manner that more effectively treats SCA in the setting of established CAD than in other pathophysiological contexts. Finally, although we

adjusted for known confounders using multivariable logist models, we cannot rule out residual confounding.

Although mechanisms of a survival benefit are not yet known, the results of this study reiterate the importance of the early diagnosis and treatment of CAD. Between 2000 and 2010, the death rate attributable to cardiovascular disease in the United States declined by 31%.⁹ This improvement was due in part to the treatment of patients with known CAD; half of a 20-year decline in cardiovascular mortality was attributed to medical therapy, of which one-third took place among patients with established CAD.¹⁰ An additional 44% of the observed mortality reduction was attributable to risk factor modification, which is heavily emphasized after a diagnosis of CAD.¹¹ While our study did not find an independent influence of cardiovascular medications on SCA survival, they represent only 1 part of an effective secondary prevention program. We could not measure the impact of physician-prescribed diet/lifestyle/exercise programs, which lower mortality rates independent of medical therapy,^{12,13} or the effect of efforts

Table 3. Evaluation of Utstein Characteristics and History of CAD/MI in Multivariable Modeling of Survival

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Age, y	0.98 (0.97 to 0.99)	<0.001	0.98 (0.96 to 0.99)	<0.001	0.98 (0.96 to 0.99)	<0.001
Female	2.0 (1.4 to 2.9)	<0.001	2.1 (1.4 to 3.1)	<0.001	2.1 (1.4 to 3.1)	<0.001
Witnessed	2.9 (1.7 to 4.8)	<0.001	2.9 (1.7 to 4.8)	<0.001	2.9 (1.7 to 4.8)	<0.001
Public location	2.1 (1.5 to 3.1)	<0.001	2.1 (1.5 to 3.0)	<0.001	2.1 (1.4 to 3.0)	<0.001
Bystander CPR	1.3 (0.9 to 1.9)	0.14	1.3 (0.92 to 1.9)	0.13	1.3 (0.93 to 2.0)	0.12
Initial rhythm VF or VT	6.5 (4.2 to 10.2)	<0.001	6.3 (4.0 to 9.8)	<0.001	6.2 (4.0 to 9.7)	<0.001
EMS system response time, min	0.94 (0.89 to 0.99)	0.03	0.94 (0.89 to 0.995)	0.02	0.94 (0.89 to 0.996)	0.04
History of CAD	—	—	1.5 (1.1 to 2.3)	0.02	—	—
History of MI	—	—	—	—	1.7 (1.1 to 2.4)	0.01

All models used 1271 patients for whom complete data sets were available (166 survivors and 1105 nonsurvivors). CAD indicates coronary artery disease; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; MI, myocardial infarction; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

to educate patients with CAD regarding how to respond to symptoms of recurrent ischemia.

Limited comparisons can be made to previous investigations. A study of in-hospital cardiac arrest among patients admitted with heart failure showed a univariate association between a history of MI and neurologically intact survival.¹⁴ One study of out-of-hospital cardiac arrest showed a univariate association between survival and prearrest history of angina,¹⁵ while others showed no association.^{16–18} Two studies assessing influence of overall comorbidity burden in patients with ventricular fibrillation arrests showed lower survival with higher burden of comorbidity.^{19,20} However, all previous out-of-hospital cardiac arrest studies evaluating comorbidities were limited by their inclusion of cardiac arrests secondary to other causes, inclusion of only patients alive at the time of hospital admission, limited accuracy of comorbidity assessment, restriction to ventricular fibrillation only, or combinations of these factors. Such studies entail prohibitive biases for many inferences regarding SCA. The evaluation of patients with variable etiologies of out-of-hospital cardiac arrest is appropriate for studies of common resuscitation algorithms, but the heterogeneity in arrest etiologies could mask important signals regarding SCA. The analysis of survival predictors in subgroups of patients who regain spontaneous circulation and survive to emergency department admission is appropriate for the study of post-arrest hospital care strategies and prognosis, but it is not appropriate for evaluating the etiology of arrests, the role of comorbidities, or the impact of initial resuscitation efforts.

Our findings will require replication in future studies. This is not yet possible, given the lack of clinical research that combines detailed adjudication of SCA (versus trauma and noncardiac causes of out-of-hospital cardiac arrest), detailed prearrest record review, and detailed information regarding resuscitation. While there is always potential for information bias in observational studies, we believe it is unlikely in this analysis because study subjects' records were ascertained regardless of comorbidity in the same manner for both survivors and nonsurvivors (as evidenced by the similarity in all major comorbidities except CAD and MI). The prescription or compliance with cardiac medications was low, but it likely reflects the reality of clinical practice in the community; in fact, only approximately 20% of patients are compliant with all cardiac medications 1 year after MI.²¹

Conclusion

Among patients who were not terminally ill, established prearrest CAD was independently associated with a 50% increase in the odds of survival after resuscitated SCA, while other comorbidities did not affect survival. These findings may have a pathophysiological basis and/or be related to the EMS

response. Given the low overall rates of survival from SCA, both mechanistic and systems-related research efforts are warranted to further investigate the link between established CAD and SCA. Regardless, these results emphasize the importance of early diagnosis and treatment of CAD in high-risk patients before catastrophic events such as SCA.

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