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Clinical paper

The association of chronic health status and survival following ventricular fibrillation cardiac arrest: Investigation of a primary myocardial mechanism

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Abstract

Introduction: Quantitative waveform measures are a surrogate of the acute physiological status of the myocardium and predict survival following ventricular fibrillation out-of-hospital cardiac arrest (OHCA). We investigated whether the amplitude spectrum area (AMSA) waveform measure mediates the adverse relationship between increasing burden of chronic health conditions and lower likelihood of survival.

Methods: We performed a cohort investigation of persons > = 18 years who suffered ventricular fibrillation OHCA between 2008–2015 in a metropolitan emergency medical service (EMS) system. The count of chronic health conditions was determined using the Charlson Comorbidity Index (CCI). AMSA was calculated just prior to the initial shock. We used multivariable logistic regression to assess the relationship between CCI and survival-to-discharge in models first without and then with AMSA to determine the extent to which AMSA attenuated the CCI-survival association.

Results: Of the 716 eligible patients, 422/716 (59%) had at least one chronic health condition; 21.8% with one, 19.6% with two, 10.3% with 3, and 7.3% with ≥4. Survival-to-discharge was 45% (324/716). In the multivariable model adjusted for traditional Utstein characteristics, increasing CCI was associated with lower odds of survival (Odds ratio (OR) (95% confidence interval] = 0.82 [0.72, 0.93] for each additional chronic health condition). The addition of AMSA to the model only modestly attenuated the CCI-survival association (OR = 0.85 [0.74,0.98]).

Conclusion: The waveform measure AMSA – a surrogate for the physiological status of the myocardium – mediated only a modest portion of the association between increasing burden of chronic health conditions and lower likelihood of survival following ventricular fibrillation OHCA.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide.[1] Considerable programmatic and research efforts are directed toward improving resuscitation. A key to improving outcomes is to understand the factors that influence resuscitation. The Utstein data elements, which include demographic, circumstance, and resuscitation care characteristics predict outcome but collectively only account for a modest portion of outcome variability.[2,3]

Increasing evidence has indicated that the burden of chronic health conditions can adversely influence prognosis.[4–6] The reasons for this association are not well-understood. One hypothesis is that chronic health conditions directly affect the myocardial substrate,

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making patients with excess chronic health conditions less responsive to treatment and hence less likely to survive following ventricular fibrillation (VF) OHCA. There is however a lack of rigorous investigation evaluating the relationship between chronic health conditions and the heart's physiologic status during VF OHCA.[7–10] Identifying the mechanism(s) by which chronic health conditions influence prognosis can improve scientific understanding of resuscitation, help explain outcome differences across populations or geographies, and potentially provide the basis to improve care.

Quantitative measures of the VF waveform are dynamic and predict outcome over the course of resuscitation.[11–14] These measures can correspond to the heart's ischemic burden and provide an assessment of energy status of the myocardial substrate.[15,16] Thus, as a surrogate for myocardial status, quantitative waveform measures provide a means to evaluate whether chronic health conditions might confer excess risk through a primary myocardial mechanism. We used the waveform measure amplitude spectrum area (AMSA) as it predicts both shock-specific ECG outcome (return of organized rhythm) and clinical outcome (return of circulation and survival to hospital discharge) across different human VF populations.[11–14] To test this theory, we hypothesized that waveform measures account for the adverse association between increasing burden of chronic health conditions and outcome following VF OHCA.

Methods

Design, study population, and setting

We performed a cohort investigation of persons 18 years or older who suffered non-traumatic OHCA and presented with ventricular fibrillation between January 1, 2008 and December 31, 2015 in a large metropolitan emergency medical service (EMS) system. Because the investigation required ECG information prior to the initial shock from the defibrillator recording, we a-priori excluded cases that received a shock from a non-EMS defibrillator i.e. public access defibrillator or law enforcement — as these would not routinely be available for review and analysis. We also excluded cases where the EMS provided the initial shock but the EMS defibrillator download was unavailable or technically not adequate (corrupted or missing ECG).

The EMS system serves a population of approximately 1.3 million persons residing in urban, suburban, and rural settings covering an area of about 2000 square miles. The EMS is a two-tiered system. The first tier is emergency medical technician-trained firefighters who provide basic life support and are equipped with automated external defibrillators. The second tier is paramedics trained in advanced life support including manual rhythm interpretation and defibrillation, intubation, and intravenous medication therapies. Resuscitation care is based on the American Heart Association guidelines.[17] Patients who are resuscitated are transported to area hospitals, each equipped with coronary catheterization and intensive care services. Hospital-based care is at the discretion of the treating physician.[18] The institutional review boards at the University of Washington and Public Health — Seattle & King County approved the study.

Data collection and definitions

The EMS system maintains an ongoing registry of all EMS-treated cardiac arrests. Information about demographics, circumstances, care, and outcome is ascertained using emergency dispatch, EMS, defibrillator, hospital and death records. The information is organized according to the Utstein Guidelines for reporting OHCA.[3] Investigators abstract information from dispatch and EMS records blinded to outcome status.

Information about pre-existing, clinically-recognized chronic health conditions was collected from the EMS reports.[19] Information from EMS records is available for all treated patients and has a fair to good kappa with hospital-based information. Inter-reviewer reliability for selected conditions has revealed a high level of agreement. The complete abstraction form including health conditions and chronic medication treatments has been previously published.[6] Chronic conditions were tallied to generate the Charlson Comorbidity Index (CCI) and categorized into 5 groups (0, 1, 2, 3 or $\geq$4) with higher numbers indicating greater burden of chronic health conditions.[20] The primary outcome was survival, as confirmed by vital status at hospital discharge.

ECG

Real-time ECG tracings were collected from the EMS defibrillator recording. ECGs were collected from MRx and ForeRunner 3 (Philips Healthcare, Bothell, WA) defibrillators and from Lifepak 12 and Lifepak 15 (Physio-Control, Redmond, WA) defibrillators. MRx ECGs were analyzed at their original sample rate of 250 Hz, ForeRunner 3 ECGs were resampled from 200 Hz to 250 Hz, and Lifepak ECGs were resampled from 125 Hz to 250 Hz. All ECG segments were bandpass-filtered from 4 to 48 Hz using a 4th-order Butterworth filter with a zero-phase implementation

AMSA calculation

We extracted a 5-s VF ECG epoch from each patient during the CPR pause immediately before the first shock. Pauses in CPR were confirmed by review of the chest impedance signal. We used these 5-s ECG epochs to generate the amplitude spectrum area (AMSA), a frequency-domain quantitative waveform measure. AMSA was calculated as $AMSA = \sum_{m=4Hz\cdot N/f_s}^{48Hz\cdot N/f_s} (X_m f_m)$, where X_m are the one-sided Discrete Fourier Transform magnitudes calculated from a Hanning-windowed VF ECG segment of N samples, f_m are the frequency values (in Hz) corresponding to each X_m magnitude, and f_s is the sampling rate[16,21–23]. As AMSA is calculated using the sum of the products of each frequency value and its corresponding magnitude, a VF ECG segment with more high-frequency content will typically have a higher AMSA value. Data extraction and processing were performed using MATLAB R2017a (The Mathworks Inc., Natick, MA).[24,25]

Statistical analysis

We used descriptive statistics to summarize categorical variables as proportions, and continuous variables as mean with standard deviation for normal distribution or as median with interquartile range for non-normal distribution. We conducted analyses to understand whether the association between chronic health conditions and survival was mediated by the AMSA waveform measure. We used logistic regression to determine the unadjusted association between Utstein parameters, chronic health conditions, and AMSA and outcome. We constructed a multivariable model that included the Utstein predictors and the CCI with CCI

being modeled as a continuous categorical variable. We then added AMSA quartile modeled as a continuous categorical variable to the multivariable model. Given the hypothesis that chronic conditions affect prognosis through a cardiac mechanism, we expected that addition of AMSA to the model would attenuate the association between chronic health conditions and outcome. We measured this contribution on a percentage basis using the equation: 1- (beta $_{chronic\ health\ conditions}$ adjusted/beta $_{chronic\ health\ conditions}$ baseline), where beta are the multivariable logistic model coefficients.[28]

Finally, we assessed for differences in the association between chronic health conditions, AMSA, and outcome among subgroups defined by witness status, age (>=65 versus <65 years), and sex by including an interaction (cross-product) term between chronic health condition group and the covariates of interest. All tests were performed using STATA/SE 14.2 (Lakeway Drive, TX, USA). A p-value < 0.05 was considered statistically significant.

Results

During the study period, 1611 persons had OHCA with an initial rhythm of VF. Of these 1611, 194 (12%) received initial defibrillation by non-EMS AED (public access or law enforcement) and were a-priori ineligible. Of the 1417 eligible patients, 554 (39%) either did not have an EMS defibrillator download or the recording was not technically sufficient, and 150 patients (11%) had no information regarding chronic health conditions, leaving 716 for the primary study cohort (Fig. 1). Compared to the primary study cohort, eligible patients who were excluded were more likely to experience the arrest in a public location and receive bystander CPR (Table 1). Overall survival to

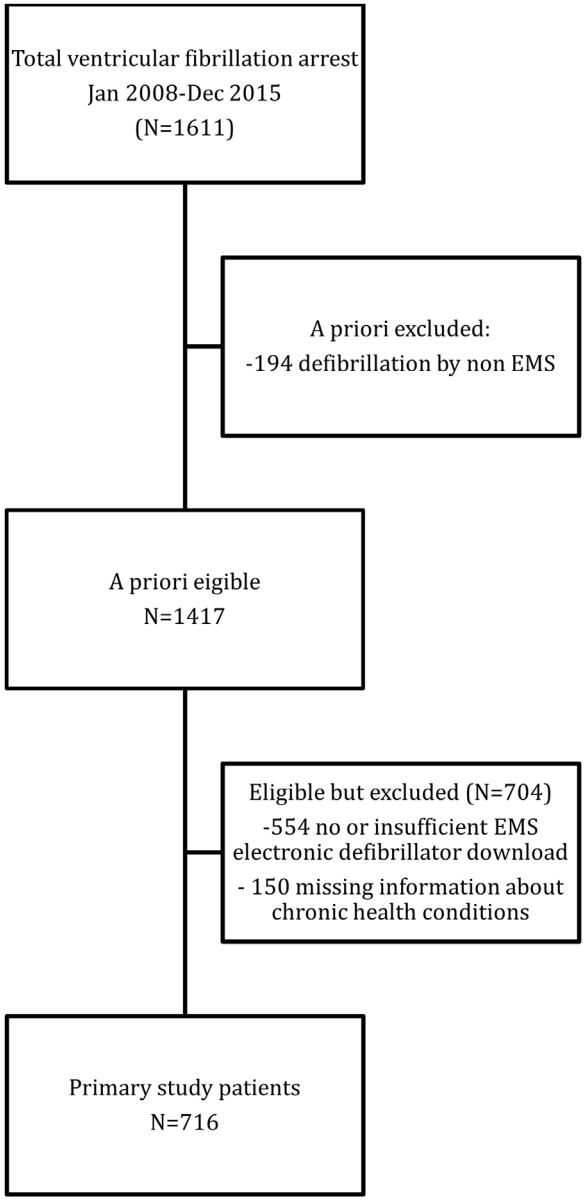

Fig. 1 – Flow chart of the study population.

Table 1 – Comparison between primary study patients and those eligible but excluded.

	Primary study cohort	Eligible excluded	
	N = 716	N = 704	
Age, years (SD)	61.8 (15.5)	63.8 (14.5)	0.10
Male gender, n (%)	540 (75)	546 (78)	0.35
Public location, n (%)	174 (24)	249 (35)	<0.001
Witnessed, n (%)	553 (77)	530 (75)	0.39
Bystander CPR, n (%)	515 (72)	442 (63)	<0.001
EMS response interval >5 min n (%)	350 (50)	338 (52)	0.44
Cardiac etiology, n (%)	663 (93)	634 (90)	0.09
CCI = 0	294 (41)	252 (40)	0.06
CCI = 1	156 (22)	125 (20)	
CCI = 2	140 (20)	119 (19)	
CCI = 3	74 (10)	57 (9)	
CCI≥4	52 (7)	75 (12)	
AMSA (SD)	7.31 (4.0)	7.52 (3.8)	0.28
Hospital survival, n (%)	324 (45)	316 (45)	0.89

discharge was 324/716 (45%) and did not differ between included and excluded patient groups.

Chronic health conditions as calculated per the CCI were observed in the majority of patients 422/716 (59%); 21.8% had one chronic health condition, 19.6% had two, 10.3% had 3, and 7.3% had 4 or more chronic health conditions. Table 2 presents the distribution of covariates according to the chronic health condition groups. As chronic health conditions increased in number, patients were increasingly older, experienced cardiac arrest in non-public area, and had longer EMS response intervals ($p < 0.05$ for trend). AMSA decreased as CCI increased ($p < 0.05$), whereas increasing AMSA quartiles were associated with younger age, public location, witnessed status, and bystander CPR performance ($p < 0.05$ for trend) (Table 3).

Table 4 presents the results of the logistic regression models. In unadjusted models, increasing CCI was associated with a decreasing likelihood of survival (trend odds ratio [OR] = 0.79 [CI = 0.70–0.89], $p < 0.001$), while increasing quartile of AMSA was associated with an increasing likelihood of survival (trend OR = 1.31 [1.24–1.37], $p < 0.001$). In the multivariable model that adjusted for Utstein predictors, increasing CCI remained associated with a lower likelihood of survival (trend OR = 0.82 (0.72–0.93], p = 0.003). When AMSA quartile was added to the multivariable model, the association between CCI and survival was attenuated only slightly (trend OR = 0.85 [0.74–0.98]). The beta for chronic health conditions was −0.202 without AMSA and −0.163 with AMSA in the multivariable model, indicating AMSA mediates 19% (1 − [beta 2/beta 1]) × 100) of the association between chronic health conditions and survival.

In sensitivity analyses, we did not observe an interaction between chronic health conditions and survival according to subgroup characteristics that had an apparent association with survival outcome (Table 4), including witnessed arrest status (p for interaction = 0.69), age (p for interaction = 0.41), or sex (p for interaction = 0.43).

Discussion

In the present cohort investigation of OHCA due to VF, an increasing burden of chronic health conditions was associated with a lower likelihood of survival after adjustment for traditional Utstein elements describing demographic, circumstance, and response characteristics. When the model also incorporated AMSA, the adverse association of chronic health conditions was attenuated only modestly and retained its independent association with survival. Collectively, the results suggest that myocardial substrate as measured by the AMSA waveform measure does not primarily mediate the association

Table 2 – Utstein and AMSA covariates according to chronic health categories.

	Charlson Comorbidity Index					
	CCI = 0 N = 294	CCI = 1 N = 156	CCI = 2 N = 140	CCI = 3 N = 74	CCI≥4 N = 52	p-Value*
Age years (SD)	56.9 (16.3)	65.4 (15.3)	64.1 (12.8)	65.6 (13)	67.4 (14.5)	<0.001
Male gender, n(%)	222 (76)	121 (78)	102 (73)	55 (74)	40 (77)	0.83
Public location, n(%)	87 (30)	39 (25)	33 (24)	13 (18)	2 (4)	<0.001
Witnessed, n(%)	223 (76)	121 (78)	117 (84)	59 (80)	33 (63)	0.74
Bystander CPR, n(%)	217 (74)	107 (69)	101 (72)	54 (73)	36 (69)	0.61
EMS Response >5 min, n(%)	129 (45)	77 (51)	72 (53)	42 (58)	30 (60)	0.009
Cardiac etiology, n(%)	269 (92)	146 (94)	134 (96)	68 (92)	46 (88)	0.99
AMSA mean (SD)	7.5 (3.9)	7.6 (4.1)	7.5 (4.4)	6.7 (3.5)	5.8 (2.8)	0.02

SD = standard deviation, CPR = cardiopulmonary ressuscitation, CCI = Charlson comorbidity index.
* p-value for trend.

Table 3 – Utstein and chronic health conditions according to AMSA quartiles.

		AMSA Quartiles				
AMSA value		**<4.20**	**4.20–6.80**	**6.80–9.60**	**>9.60**	p-Value
		N = 187	N = 180	N = 174	N = 175	
Age, years (SD)		63.8 (15.2)	62.9 (15.4)	61.9 (16.2)	58.5 (14.9)	0.008
Male gender, n(%)		149 (80)	138 (77)	124 (71)	129 (74)	0.10
Public location, n(%)		34 (18)	34 (19)	48 (28)	58 (33)	<0.001
Witnessed, n(%)		117 (63)	139 (77)	146 (84)	151 (86)	<0.001
Bystander CPR, n(%)		117 (63)	127 (71)	131 (75)	140 (80)	<0.001
EMS response >5 min, n(%)*		85 (24)	86 (25)	90 (26)	89 (25)	0.46
Cardiac etiology, n(%)		171 (91)	165 (92)	161 (93)	166 (95)	0.21
CCI	**0**	73 (39)	72 (40)	71 (41)	78 (45)	0.048
	1	40 (21)	30 (17)	48 (28)	38 (22)	
	2	33 (18)	42 (23)	27 (16)	38 (22)	
	3	23 (12)	19(11)	19 (11)	13 (7)	
	≥4	18 (10)	17 (9)	9 (5)	8 (5)	

Bold values are related to AMSA quartiles that are determining the different category.
* dichotomized according to the median, SD = standard deviation, CPR = cardiopulmonary ressuscitation, CCI = Charlson comorbidity index.

Table 4 – Logistic regression predicting survival at discharge.

	Unadjusted odds ratio of survival			Multivariable odds ratio of survival					
				Utstein-only adjusted			Utstein and AMSA adjusted		
	OR	95% CI	p-Value	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	0.97	(0.96–0.98)	<0.001	0.97	(0.96–0.98)	<0.001	0.97	(0.96–0.98)	<0.001
Male gender	0.75	(0.54–1.06)	0.10	0.69	(0.48–1.0)	0.05	0.75	(0.50–1.11)	0.15
Public location	1.50	(1.06–2.11)	0.02	1.04	(0.72–1.52)	0.82	0.84	(0.56–1.27)	0.41
Witnessed	2.77	(1.89–4.07)	<0.001	2.56	(0.70–3.86)	<0.001	1.99	(1.28–3.08)	0.002
Bystander CPR	1.22	(0.87–1.69)	0.25	1.29	(0.89–1.85)	0.18	0.97	(0.65–1.45)	0.89
EMS Response time <5 min	1.42	(1.05–1.92)	0.02	1.53	(1.10–2.13)	0.01	1.43	(1.01–2.04)	0.045
Cardiac etiology	2.45	(1.30–4.59)	0.005	3.27	(1.60–6.69)	0.001	2.99	(1.39–6.45)	0.005
CCI	0.78	(0.70–0.89)	<0.001	0.82	(0.72–0.93)	0.003	0.85	(0.74–0.98)	0.025
AMSA	1.31	(1.24–1.37)	<0.001	—	——	———	1.27	(1.20–1.34)	<0.001

between an increasing burden of chronic health conditions and lower likelihood of survival following VF arrest, suggesting that other alternative mechanisms should be considered.

Prior research has demonstrated that the Utstein elements are important predictors but are not sufficient to explain outcome differences within or across systems, and collectively account for only a modest proportion of the variability in survival.[2,29] The results of current and prior investigations indicate that incorporating chronic health conditions can improve prediction. In the present study, an increasing burden of chronic health conditions was associated with a reduced likelihood of survival in a dose-dependent fashion. The question then is what mechanisms might mediate this adverse risk given that all patients in the current cohort presented with VF ventricular fibrillation in a model that was adjusted for Utstein characteristics?

In this study, we investigated whether a primary myocardial mechanism might explain the association between comorbidity and OHCA outcome. We hypothesized that chronic health conditions might affect the intrinsic myocardial expression of VF. Specifically, we used the AMSA quantitative waveform measure derived from the ECG captured just prior to the initial shock. Previous research suggests that waveform measures such as AMSA might serve as a surrogate for coronary perfusion pressure and myocardial energy during resuscitation.[7,8] Indeed we observed a strong and independent relationship between increasing AMSA and a greater likelihood of survival. However, inclusion of AMSA in the multivariable model accounted for only a modest proportion of the adverse relationship between chronic health conditions and outcome, suggesting that other mechanisms account for the association.

Other mechanisms might include variability in pre-hospital emergency medical services (EMS) interventions, which could differ according to chronic health status. Although the Utstein elements include categorical EMS measures, there may be differences in quantitative aspects of care such as the timing and quality of bystander and EMS CPR. Alternatively, hospital care may differ according to the burden of chronic health conditions, and could influence the types and extent of hospital intervention and support.

The current study has limitations. Specifically we were not able to evaluate more detailed potential mediators to include the aforementioned quantitative prehospital measures of resuscitation or in-hospital care. We used a clinical outcome (survival) that is several steps removed from the initial waveform measure. The use of more proximal outcome could reveal different relationships among CCI, AMSA, and intermediate outcomes such as organized rhythm

following the shock. The study used an observational design. Thus caution must be exercised in attributing cause-and-effect outcome relationships as it relates to chronic health conditions and AMSA, though these findings were adjusted for potential confounders. Chronic health conditions in this study were ascertained by EMS providers. Although this approach may underestimate the prevalence of comorbidity, it captures this information in all patients, including those who did not survive to hospital admission and whose comorbidities might not otherwise be known. Moreover the accuracy of this methodology has been validated when compared with hospital-sourced information.[19] The current study evaluates cumulative comorbidity as measured by the Charlson Index and does not investigate a specific comorbidity, its influence on outcome, or whether this relationship may be mediated by primary cardiac mechanism as measured by the AMSA waveform. Indeed specific comorbidities may have distinct mechanisms influencing outcome. We used AMSA as a surrogate of myocardial status given this waveform measure is well-tested as a predictor of outcome. Other waveform measures, or alternative surrogates for myocardial status, may have produced different results. Finally, the results come from a mature metropolitan EMS system that achieves a relatively high survival such that the results may not be generalizable to all communities. These limitations should be balanced with the investigation's strengths; a well-characterized cohort of persons with VF arrest that incorporated quantitative waveform measures to evaluate novel relationships potentially responsible for resuscitation mechanisms.

Conclusions

An increasing burden of chronic health conditions was associated with a lower likelihood of survival following VF OHCA independent of traditional Utstein predictors. The quantitative waveform measure AMSA– a surrogate for the physiological status of the myocardium– accounted for only a modest portion of the association between chronic health conditions and outcome, suggesting other mechanisms are likely responsible for this association. Future study should investigate alternative mechanisms to account for this association as a means to understand heterogeneity of outcome and potentially help improve resuscitation care.

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