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ORIGINAL RESEARCH

Insights From the Ventricular Fibrillation Waveform Into the Mechanism of Survival Benefit From Bystander Cardiopulmonary Resuscitation

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BACKGROUND: The mechanism by which bystander cardiopulmonary resuscitation (CPR) improves survival following out-of-hospital cardiac arrest is unclear. We hypothesized that ventricular fibrillation (VF) waveform measures, as surrogates of myocardial physiology, mediate the relationship between bystander CPR and survival.

METHODS AND RESULTS: We performed a retrospective cohort study of adult, bystander-witnessed patients with out-of-hospital cardiac arrest with an initial rhythm of VF who were treated by a metropolitan emergency medical services system from 2005 to 2018. Patient, resuscitation, and outcome variables were extracted from emergency medical services and hospital records. A total of 3 VF waveform measures (amplitude spectrum area, peak frequency, and median peak amplitude) were computed from a 3-second ECG segment before the initial shock. Multivariable logistic regression estimated the association between bystander CPR and survival to hospital discharge adjusted for Utstein elements. Causal mediation analysis quantified the proportion of survival benefit that was mediated by each VF waveform measure. Of 1069 patients, survival to hospital discharge was significantly higher among the 814 patients who received bystander CPR than those who did not (0.52 versus 0.43, respectively; $P<0.01$). The multivariable-adjusted odds ratio for bystander CPR and survival was 1.6 (95% CI, 1.2, 2.1), and each VF waveform measure attenuated this association. Depending on the specific waveform measure, the proportion of mediation varied: 53% for amplitude spectrum area, 31% for peak frequency, and 29% for median peak amplitude.

CONCLUSIONS: Bystander CPR correlated with more robust initial VF waveform measures, which in turn mediated up to one-half of the survival benefit associated with bystander CPR. These results provide insight into the biological mechanism of bystander CPR in VF out-of-hospital cardiac arrest.

Key Words: bystander CPR ■ mediation analysis ■ resuscitation ■ ventricular fibrillation waveform

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death worldwide.[1] Early cardiopulmonary resuscitation (CPR) initiated by laypeople before arrival of professional rescuers is associated with a greater likelihood of survival and functional recovery.[2,3] However, the physiologic mechanisms by which bystander CPR confers a survival advantage are not clear, and a better understanding of these mechanisms could provide insight toward improving CPR performance and effectiveness. Proposed mechanisms include enhanced cerebral blood flow, improved coronary perfusion and myocardial energy stores, reduction of right heart distension, ischemic postconditioning, and some measure of passive ventilation.[4–6] Alternatively, the bystander CPR–survival association may be related to residual confounding, as

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CLINICAL PERSPECTIVE

What Is New?

- Bystander cardiopulmonary resuscitation (CPR), including both unassisted CPR and telephone-assisted CPR, correlated with more robust initial ventricular fibrillation waveform measures following witnessed, ventricular fibrillation out-of-hospital cardiac arrest.
- Depending on the specific ventricular fibrillation waveform measure, roughly one-quarter to one-half of the survival benefit associated with bystander CPR was mediated by ventricular fibrillation waveform measures.

What Are the Clinical Implications?

- Much of the survival benefit conferred by bystander CPR may be related to its effect on the myocardium.
- These data may provide novel considerations into how waveform measures might be incorporated to help assess the effectiveness of CPR.

Nonstandard Abbreviations and Acronyms

AMSA	amplitude spectrum area
OHCA	out-of-hospital cardiac arrest
TCPR	telephone-assisted CPR

the provision of bystander CPR is related to prognostic factors such as witnessed status, arrest location, and the perceived viability of the patient.[7–10]

Quantitative measures of the ventricular fibrillation (VF) ECG signal are mathematical functions that characterize ECG features such as frequency, organization, and amplitude. A variety of measures have been designed with the ultimate goal of developing more effective treatment strategies for patients with VF. These measures are associated with dynamic changes in myocardial energy stores (adenosine triphosphate concentrations) and coronary perfusion pressure during the course of resuscitation, and predict clinical outcomes such as responsiveness to shock and functional survival.[11–14] Quantitative measures of the VF waveform thus potentially reflect physiologic status and provide a means to evaluate how interventions, such as CPR and medications, affect the heart during resuscitation and possibly mediate survival.[15,16]

To investigate mechanisms by which bystander CPR may improve outcome, we evaluated the association between bystander CPR, VF waveform measures, and survival in patients with a witnessed OHCA and an initial rhythm of VF. We hypothesized that the association between bystander CPR (provided with or without telecommunicator assistance) and outcome is mediated by VF waveform measures independent of Utstein OHCA characteristics.

METHODS

The Institutional Review Board for Human Subjects Research at the University of Washington and the Department of Public Health–Seattle and King County approved this study and determined that it was minimal risk and waived informed consent. The data that support the findings of this study, with the exception of patient ECG data, are available from the corresponding author upon reasonable request.

Study Design, Population, and Setting

We performed a retrospective cohort investigation of adults with nontraumatic, bystander-witnessed OHCA who presented with an initial rhythm of VF and were treated by a single emergency medical services (EMS) system from 2005 to 2018. The cohort was restricted to bystander-witnessed arrests because VF waveform measures degrade over time without CPR, and the inclusion of unwitnessed arrests might therefore confound the association between bystander CPR and the initial VF waveform measure value.[17,18] Patients were included if there was an available EMS electronic defibrillator recording with ECG and transthoracic impedance signals before the first shock, and this shock was preceded by a pause in CPR of at least 3 seconds. Patients were excluded if (1) a shock was delivered by public access or law enforcement defibrillator before EMS arrival or (2) there was electrical artifact from pacing or other sources visible in the ECG.

The EMS system of the study region serves a population of ≈1.5 million people residing in urban, suburban, and rural settings covering an area of ≈2000 square miles. The EMS system is a 2-tiered system that is activated by calling 9-1-1. Emergency medical dispatchers dispatch care and, if CPR is not already in progress, instruct bystanders to perform chest compressions without rescue breathing. The first tier of the EMS system consists of emergency medical technicians trained in basic life support and equipped with automated external defibrillators. Emergency medical technicians respond to all emergency medical calls and usually arrive first on scene an average of 5 minutes after call receipt. The second tier consists of paramedics trained in advanced life support who arrive on average 8 minutes after call receipt. Paramedics respond to selected, more serious conditions such as OHCA. EMS rescuers are instructed to start or continue CPR, analyze the rhythm, and, if indicated, defibrillate as

soon as possible after application of the defibrillator. Resuscitation care is based on the American Heart Association guidelines.[19]

Data Collection and Definitions

The EMS system maintains an ongoing registry of all EMS-treated OHCA organized according to the Utstein guidelines.[20] These registry data include demographic, arrest circumstance, resuscitation process, and clinical outcome data collected from the EMS report, emergency dispatch audio recording, electronic defibrillator recording, and hospital record. Because these data include potentially identifiable information, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Bystander CPR was defined as the provision of chest compressions, with or without ventilations, by a person not responding as part of the organized 9-1-1 response EMS system. Bystander CPR was classified into 2 groups: (1) telephone-assisted CPR (TCPR) if the telecommunicator provided specific instructions regarding compressions to the bystander or (2) unassisted CPR if telecommunicator instructions were not involved with the provision of CPR. EMS response interval was defined as the time of emergency call pickup to arrival time of the first EMS unit. Because the cohort was restricted to witnessed arrests, the EMS response interval was presumed to approximate the time from arrest to EMS arrival. Sustained return of spontaneous circulation (ROSC) was defined as a palpable pulse and measurable blood pressure for 20 consecutive minutes or until emergency department arrival. Neurologically intact survival was defined as survival to hospital discharge with a Cerebral Performance Category of 1 or 2.[20]

ECG Data and Calculation of VF Waveform Measures

Investigators, blinded to bystander CPR status and clinical outcomes, used MATLAB (Mathworks, Natick, MA) software to review the ECG and transthoracic impedance signals from the defibrillator recording to extract an artifact-free, 3-second ECG segment during a chest compression pause before the initial shock. Defibrillator models included Forerunner 3, Heartstart MRx (Philips Healthcare, Bothell, WA) and Lifepak 12 and Lifepak 15 (Stryker Physio-Control, Redmond, WA). ECG sampling rates ranged from 125 to 250 Hz across devices; signals at an original sampling rate <250 Hz were resampled to 250 Hz. Each segment was filtered to remove high-frequency noise and baseline drift using a 1 to 30 Hz fourth-order Butterworth bandpass filter with forward-backward implementation.

We calculated 3 VF waveform measures from the 3-second ECG segments since the degree of mediation potentially varied across measures: amplitude spectrum area (AMSA), peak frequency, and median peak amplitude (Figure 1).[21–23] AMSA was computed from the discrete Fourier transform of the Hanning-windowed ECG as the sum of each frequency from 3 to 30 Hz multiplied by its magnitude. Peak frequency was defined as the frequency with the greatest power between 1 and 20 Hz on the discrete Fourier transform of the rectangular-windowed ECG. The median peak amplitude of the ECG was defined as the absolute difference between the median amplitude of the highest 4 peaks and the median amplitude of the lowest 4 valleys.

Statistical Analysis

We used descriptive statistics to summarize demographic, resuscitation process, and clinical outcome variables. The study cohort and excluded cohort were compared using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Patients who did and did not receive bystander CPR were compared in a similar manner, as were the bystander CPR subgroups (TCPR and unassisted CPR).

We calculated unadjusted odds ratios for the association between each Utstein element and survival to hospital discharge and computed CIs using the Fisher's exact method for dichotomous variables (bystander CPR, sex, etiology, and location) and logistic regression for continuous variables (age and EMS response time). To investigate the mechanism of the bystander CPR–survival association, we then fit a multivariable logistic regression model with the aforementioned Utstein elements as predictor variables (termed the *Utstein model*) to calculate the adjusted odds ratio between bystander CPR and this outcome. Each VF measure was then added individually as a predictor variable to the Utstein model; these expanded models were denoted as the mediation models. According to the hypothesized mechanism (Figure 2), bystander CPR may affect survival via the VF waveform measure and via other non-waveform-mediated pathways. Attenuation of the regression coefficient for bystander CPR in the mediation model compared with the Utstein model would provide qualitative evidence for mediation.[24]

To quantify the degree of mediation, we then conducted a causal mediation analysis with each of the VF waveform measures as a potential mediator.[25] Causal mediation analysis is preferred over other types of mediation analysis (such as the difference and product-of-coefficients methods) when there are nonlinear relationships or a prevalent binary outcome, which was

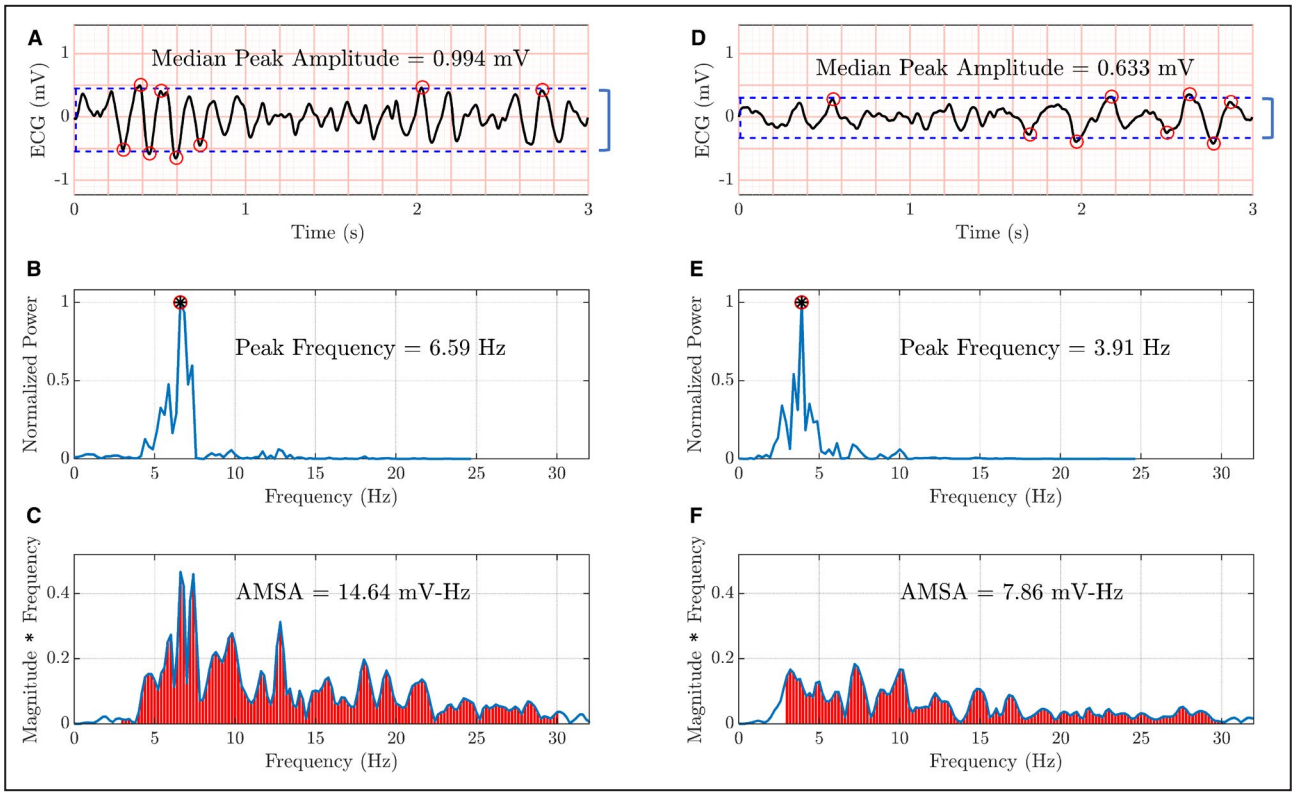

Figure 1. Examples of 3-second ECG segments with corresponding ventricular fibrillation waveform measures.
The subplots in the left column (**A** through **C**) show the median peak amplitude, peak frequency, and amplitude spectrum area (AMSA), respectively, for the ECG segment in subplot (**A**). The subplots in the right column (**D** through **F**) show the corresponding ventricular fibrillation waveform measures for the ECG segment in subplot (**D**). The ECG segment on the left has higher, that is, more favorable, ventricular fibrillation waveform measures. Please see text for details of ventricular fibrillation waveform measure calculation.

the case with this data set.[24,26] In this approach, the effect of an exposure on an outcome is partitioned into mediated (ie, indirect) and nonmediated (ie, direct) effects. Regression models of the intervention–mediator and mediator–outcome associations are fit, and the regression coefficients are used to simulate values of the mediator and outcome in hypothetical scenarios in which patients do and do not receive the intervention.[26,27] The simulated (nonobserved) and observed values are used to calculate mediated and nonmediated effects. The proportion mediated is the mediated effect divided by the sum of the mediated and nonmediated effects.

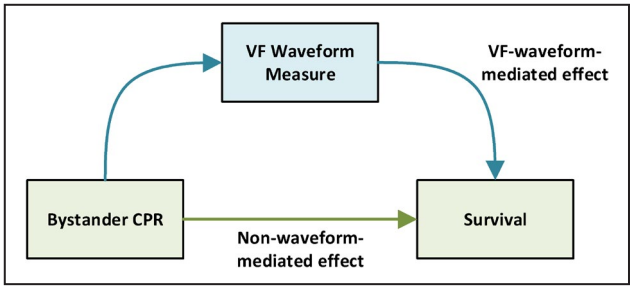

Figure 2. Hypothesized VF waveform-mediated pathway.
CPR indicates cardiopulmonary resuscitation; and VF, ventricular fibrillation.

Following the aforementioned approach, we fit the following 2 regression models: (1) a multivariable linear regression model with the Utstein elements as the predictors and the VF waveform measure as the outcome and (2) the previously described mediation model with survival as the outcome.[25] The waveform-mediated and the non-waveform-mediated effects were estimated from these regression models using the *mediate*function of the R package *mediation*.[28] The waveform-mediated effect was defined as the absolute difference in survival that resulted from a change in the VF waveform measure value from the no-bystander CPR group mean to the bystander CPR group mean. The non-waveform-mediated effect was defined as the absolute difference in survival from receiving bystander CPR but without a corresponding change in the VF waveform measure value.

As secondary analyses, we repeated the aforementioned regression and causal mediation analyses first by using neurologically intact survival (Cerebral Performance Category 1 or 2) as the outcome and, second, by analyzing the TCPR and unassisted CPR subgroups separately.

A *P* value of 0.05 was considered statistically significant, and no adjustment was made for multiple comparisons. The statistical analysis was performed with R version 3.6.2.

RESULTS

From 2005 to 2018, 1953 adults had a bystander-witnessed, nontraumatic OHCA with a presenting rhythm of VF, 237 of whom were ineligible because of a shock received before EMS arrival. Of the remaining 1716 patients, we were able to extract a 3-second pre-shock VF segment from 1072 patients (Figure 3). The 644 excluded patients were older, less likely to present with a cardiac etiology, and less likely to survive to hospital discharge, but did not differ in other characteristics including bystander CPR status (Table S1). In the study cohort, 814 (76%) patients received bystander CPR before EMS arrival. We did not observe statistical differences in the distribution of Utstein characteristics according to bystander CPR status with the exception of longer average EMS response interval (5.3 minutes in the bystander CPR group versus 5.0 minutes in the no-bystander CPR group) and fewer median number of shocks (3 in the bystander CPR group versus

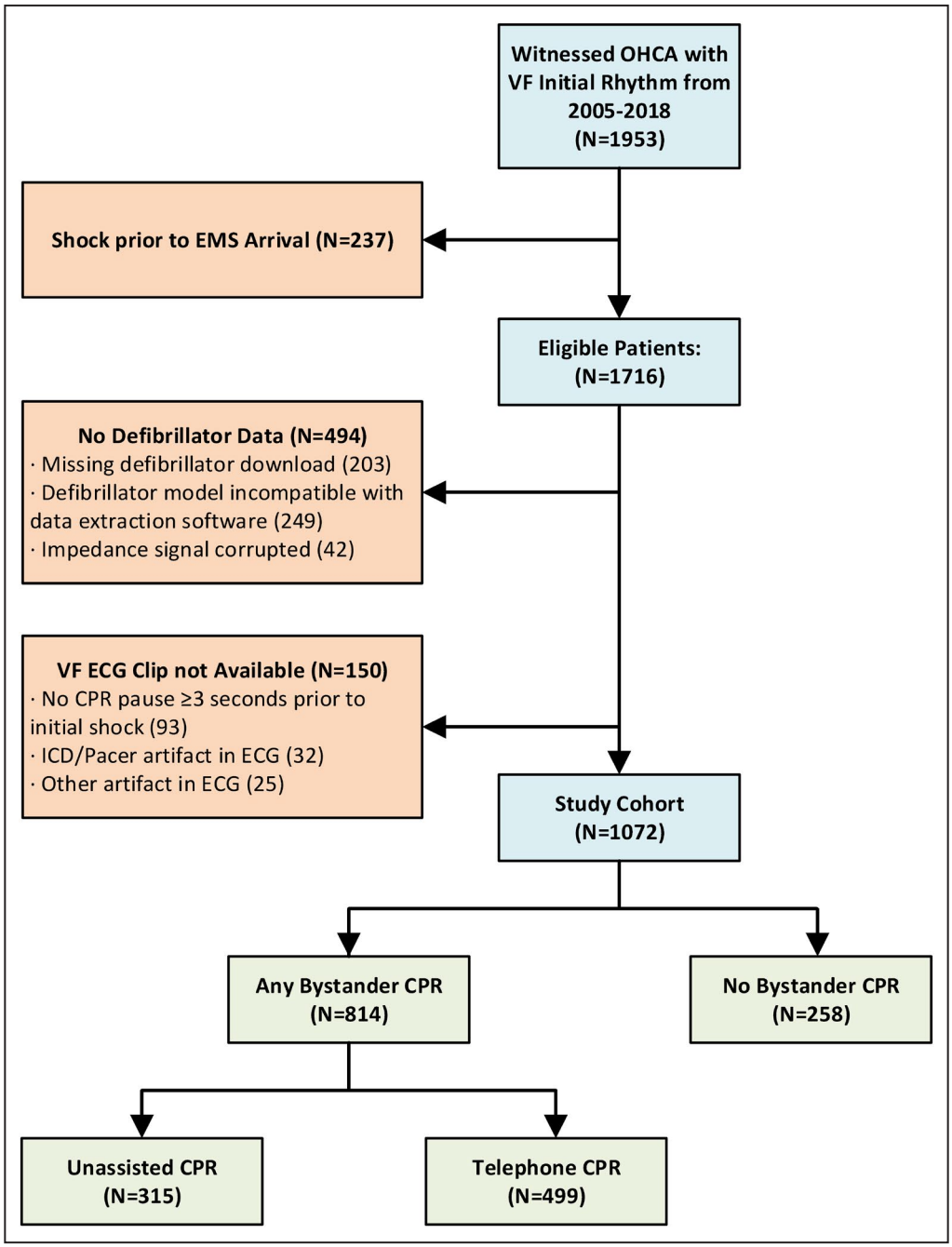

Figure 3. Selection of study population and classification according to bystander CPR status. CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; ICD, implantable cardioverter-defibrillator; OHCA, out-of-hospital cardiac arrest; and VF, ventricular fibrillation.

4 shocks in the no-bystander CPR group; Table 1). The 3 VF waveform measures before the first shock—AMSA, peak frequency, and median peak amplitude—were significantly higher in recipients of bystander CPR than no-bystander CPR ($P<0.01$ for each comparison; Table 1) as were sustained ROSC (77% versus 67%), admission rate to the hospital (75% versus 68%), survival to hospital discharge (52% versus 43%; $P<0.01$), and neurologically intact survival (48% versus 37%; $P<0.01$) in the 2 respective groups.

Among patients who received bystander CPR, 499 (61%) required TCPR, and in 315 (39%), CPR was unassisted (Table 1). Patients comprising the unassisted CPR subgroup were on average younger, more likely to arrest in public, and had a shorter average EMS response interval than TCPR recipients. The VF waveform measures were significantly higher in each bystander CPR subgroup than the no-bystander CPR group ($P<0.01$ for each comparison). VF waveform measures and all clinical outcomes (sustained ROSC, admission to hospital, survival to hospital discharge, and neurologically intact survival) were not significantly different between the assisted and unassisted CPR subgroups.

Bystander CPR was associated with greater likelihood of survival to hospital discharge compared with no-bystander CPR in the unadjusted model (odds ratio, 1.5; 95% CI, 1.1–2.0) and in the multivariable adjusted Utstein model (odds ratio, 1.6; 95% CI, 1.2–2.1; Table 2). The addition of each waveform measure attenuated the association between bystander CPR and survival. In the causal mediation analysis, bystander CPR was significantly associated with higher VF waveform measures after adjustment for the other Utstein variables (Table S2). AMSA, peak frequency, and median peak amplitude mediated 53%, 31%, and 29%, respectively, of the association between bystander CPR and survival (Table 3).

In the secondary analyses, the regression and mediation analyses results were similar using neurologically intact survival rather than survival to hospital discharge as the outcome (Tables 2 and 3). We observed similar patterns when bystander CPR was stratified into the TCPR and unassisted CPR subgroups (Table 3 and Table S3).

DISCUSSION

In this cohort of bystander-witnessed OHCA presenting with an initial rhythm of VF, ≈three-quarters of the 1072 patients received bystander CPR and half survived to hospital discharge. Survival to hospital discharge was about 10% higher in the bystander CPR group than the no-bystander CPR group (52% versus 43%), as was neurologically intact survival (48% versus 37%), associations that were independent of other Utstein characteristics. Bystander CPR status corresponded to a more robust set of initial VF waveform measures—suggesting more favorable myocardial physiology—that in turn may represent a pathway by which bystander CPR improved outcome.

Epidemiologic health services evaluation among human OHCA have demonstrated a beneficial association between bystander CPR and clinical outcomes.[2] Our understanding of the biologic mechanisms by which CPR may affect clinical outcomes, however, has generally relied on animal studies. In swine models of VF arrest, measured characteristics of the VF waveform corresponded to the duration of untreated arrest, the myocardial energy status of the heart, and the likelihood of survival.[17] In a rat model of VF arrest, CPR was able to stabilize and improve myocardial energy status at least transiently.[29] However, translation to human experience has been challenging. In 2 prior studies of 77 and 134 patients, the relationship of EMS CPR with VF waveform measures varied depending on the specific measure, the statistical methodology, and the duration of CPR.[18,30] No human study has yet investigated the mechanistic biology of bystander CPR and how it may mediate clinical outcomes.

The lack of such evidence has led some to question bystander CPR as a public health intervention, suggesting that bystander CPR is simply a confounding marker for a well-trained bystander who can activate 9-1-1 more quickly.[7] The current results, however, found that bystander CPR was associated with improved VF waveform measures regardless of the type of bystander CPR. Indeed, the observation that recipients of TCPR experienced a similar benefit as those who received unassisted CPR suggests that bystander CPR is not merely a confounder. Bystanders who require telecommunicator assistance are less likely to comprise a group of well-trained, quick-responding bystanders; rather, they likely constitute a more naïve group that is challenged to recognize and respond to cardiac arrest. The current results provide useful evidence that bystander CPR can produce a beneficial biological effect on the myocardium as reflected by waveform measures.

Ventricular fibrillation waveform measures have been associated with myocardial physiological status (adenosine triphosphate stores), suggesting that bystander CPR may work to improve survival through a primary cardiac mechanism.[31,32] Although perhaps not surprising, the current results help validate experimental research demonstrating CPR mechanisms related to coronary perfusion and oxygen delivery and their influence on myocardial energetics.[33–35] The VF waveform measures mediated between a quarter to half of the survival benefit, depending on the specific measure. The observed variability in degree of mediation

Table 1. Patient Characteristics, Resuscitation Process Variables, VF Waveform Measures, and Clinical Outcomes According to Bystander CPR Status

	Bystander CPR			Bystander CPR subgroups		
	Any	None	*P* Value	Telephone CPR	Unassisted CPR	*P* Value
Total patients, n	814	258		499	315	
Patient characteristics						
Female patients, n (%)	179 (22)	46 (18)	0.18	112 (22)	67 (21)	0.76
Age, y, median (IQR)	62 (52–72)	61 (53–74)	0.47	63 (54–72)	60 (51–71)	0.013
Cardiac etiology, n (%)	778 (96)	245 (95)	0.81	479 (96)	299 (95)	0.58
Public location, n (%)	276 (34)	94 (36)	0.50	95 (19)	181 (57)	<0.01
Resuscitation process variables						
EMS response time, min, median (IQR)	5.3 (4.2–6.8)	5.0 (4.0–6.0)	<0.01	5.6 (4.6–7.0)	5.0 (4.0–6.0)	<0.01
Interval between device power to ECG segment, seconds, median (IQR)	37 (20–61)	38 (20–59)	0.88	41 (23–66)	31 (17–57)	<0.01
Shocks delivered, median (IQR)	3 (1–6)	4 (2–7)	<0.01	3 (1–6)	3 (1–5)	0.50
VF waveform measures						
AMSA, median (IQR)	9.8 (6.6–14) mV-Hz	7.5 (4.6–11) mV-Hz	<0.01	10.0 (6.8–14) mV-Hz	9.4 (6.1–13) mV-Hz	0.15
Peak frequency, median (IQR)	4.6 (3.2–6.1) Hz	3.9 (2.9–5.4) Hz	<0.01	4.6 (3.2–6.4) Hz	4.6 (3.2–6.1) Hz	0.47
Median peak amplitude, median (IQR)	0.80 (0.55–1.1) mV	0.67 (0.44–0.94) mV	<0.01	0.80 (0.57–1.1) mV	0.76 (0.54–1.0) mV	0.18
Clinical outcomes						
Sustained ROSC, n (%)	626 (77)	173 (67)	<0.01	402 (81)	251 (80)	0.70
Admit to hospital, n (%)	612 (75)	176 (68)	0.03	380 (76)	232 (74)	0.47
Survive to hospital discharge, n (%)	425 (52)	110 (43)	<0.01	265 (53)	160 (51)	0.57
Neurologically intact survival, Cerebral Performance Category 1 or 2, n (%)*	392 (48)	96 (37)	<0.01	244 (49)	148 (47)	0.67

AMSA indicates amplitude spectrum area; CPR, cardiopulmonary resuscitation; IQR, interquartile range; ROSC, return of spontaneous circulation; and VF, ventricular fibrillation.

*Cerebral performance category was missing for 4 patients in the no-bystander CPR group and 1 patient in the bystander CPR group (unassisted CPR subgroup).

may be related to the measures' inherent abilities to quantify myocardial physiology. AMSA incorporates both amplitude and frequency of the VF waveform, and in a prior study, AMSA was a more accurate predictor of patient outcome than more basic measures of VF frequency alone (such as peak frequency), which in turn were more accurate than measures of VF amplitude alone (such as median peak amplitude).[11]

One interpretation of these findings is that none of the selected VF waveform measures optimally reflect the myocardial substrate; it is possible that these waveform measures together mediate a greater proportion of the survival benefit when acting jointly or that alternative waveform measures (such as measures that apply machine learning to improve performance) could serve as more effective mediators.[36] Alternatively, the mechanism by which bystander CPR conveys survival benefit may be distinct from the waveform.[37] Certainly, downstream care by EMS or at the hospital also influences outcome. In addition, bystander CPR may mediate a survival benefit through other mechanisms, most notably cerebral perfusion and oxygenation, that may not be captured by cardiac waveform measures.

Table 2. Adjusted and Unadjusted Odds Ratios for Predicting Clinical Outcomes

Outcome	Variable	Unadjusted	Utstein model	Mediation models		
				AMSA	Peak frequency	Median peak amplitude
Survival to hospital discharge	Utstein elements					
	Bystander CPR	1.5 (1.1–2.0)	1.6 (1.2–2.1)	1.3 (0.92–1.7)	1.4 (1.0–1.9)	1.4 (1.0–1.9)
	Female patients	1.4 (1.0–1.9)	1.4 (1.0–1.9)	1.3 (0.96–1.9)	1.2 (0.89–1.7)	1.4 (0.99–1.9)
	Public vs private location	1.4 (1.0–1.8)	1.1 (0.80–1.4)	0.93 (0.70–1.2)	0.98 (0.74–1.3)	0.99 (0.75–1.3)
	Cardiac	1.8 (0.94–3.4)	2.8 (1.5–5.5)	2.7 (1.4–5.4)	2.5 (1.3–5.1)	2.9 (1.5–5.8)
	Age/10	0.71 (0.65–0.78)	0.69 (0.63–0.76)	0.69 (0.62–0.76)	0.69 (0.63–0.76)	0.69 (0.62–0.75)
	EMS response time	0.85 (0.79–0.90)	0.84 (0.78–0.89)	0.84 (0.79–0.90)	0.85 (0.80–0.91)	0.85 (0.79–0.90)
	VF waveform measures					
	AMSA	2.0 (1.7–2.3)		1.9 (1.7–2.2)		
	Peak frequency	2.0 (1.7–2.3)			1.8 (1.6–2.1)	
	Median peak amplitude	1.6 (1.4–1.8)				1.5 (1.3–1.7)
Neurologically intact survival (Cerebral Performance Category 1 or 2)	Utstein elements					
	Bystander CPR	1.5 (1.1–2.1)	1.7 (1.2–2.3)	1.3 (0.95–1.8)	1.5 (1.1–2.0)	1.5 (1.1–2.0)
	Female patients	1.2 (0.85–1.6)	1.1 (0.82–1.5)	1.1 (0.75–1.5)	0.97 (0.69–1.3)	1.1 (0.79–1.5)
	Public vs private	1.6 (1.2–2.0)	1.2 (0.93–1.6)	1.1 (0.81–1.4)	1.1 (0.85–1.5)	1.1 (0.87–1.5)
	Cardiac	1.8 (0.94–3.5)	2.7 (1.4–5.5)	2.6 (1.3–5.4)	2.5 (1.2–5.0)	2.8 (1.5–5.7)
	Age/10	0.70 (0.64–0.77)	0.69 (0.62–0.76)	0.69 (0.62–0.76)	0.69 (0.62–0.76)	0.69 (0.62–0.76)
	EMS response time	0.85 (0.79–0.90)	0.84 (0.78–0.89)	0.84 (0.79–0.90)	0.85 (0.79–0.91)	0.85 (0.79–0.91)
	VF waveform measures					
	AMSA	2.1 (1.8–2.4)		2.0 (1.7–2.3)		
	Peak frequency	2.1 (1.8–2.4)			2.0 (1.7–2.3)	
	Mean peak amplitude	1.6 (1.4–1.8)				1.5 (1.3–1.7)

The Utstein model includes bystander CPR, sex, location, etiology, age, and EMS response time as predictor variables. The mediation models include a single VF measure in addition to the Utstein variables. VF waveform measures were log-transformed and standardized; 95% CIs are in parentheses. AMSA indicates amplitude spectrum area; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; and VF, ventricular fibrillation. Age/10 is the age in years divided by 10.

Table 3. Results of Causal Mediation Analysis With Different Categorizations of Bystander CPR as the Intervention, Different VF Waveform Measures as Potential Mediators, and Survival to Hospital Discharge and Neurologically Intact Survival as the Outcomes

Comparison	Outcome	Parameter	Mediator		
			AMSA	Peak frequency	Mean peak amplitude
Any bystander CPR vs no CPR	Survival to hospital discharge	VF waveform-mediated effect	0.053	0.031	0.029
		Non-waveform-mediated effect	0.047	0.071	0.072
		Proportion mediated	0.53	0.31	0.29
Any bystander CPR vs no CPR	Neurologically intact survival	VF waveform-mediated effect	0.054	0.030	0.028
		Non-waveform-mediated effect	0.055	0.080	0.080
		Proportion mediated	0.50	0.29	0.25
Telephone CPR vs no CPR	Survival to hospital discharge	VF waveform-mediated effect	0.067	0.038	0.036
		Non-waveform-mediated effect	0.065	0.097	0.098
		Proportion mediated	0.51	0.28	0.27
Unassisted CPR vs no CPR	Survival to hospital discharge	VF waveform-mediated effect	0.032	0.020	0.017
		Non-waveform-mediated effect	0.029	0.041	0.045
		Proportion mediated	0.52	0.33	0.27

Effect sizes are expressed as absolute differences in survival. AMSA indicates amplitude spectrum area; CPR, cardiopulmonary resuscitation; and VF, ventricular fibrillation.

The direct relationship between binary (yes/no) bystander CPR and quantitative waveform measures also supports the potential to consider the waveform as a gauge of the quality of bystander CPR. Currently, we are challenged to assess the effectiveness of different approaches to bystander CPR. Although speculative, one approach among patients with VF OHCA might be to evaluate the initial and evolving value of the VF waveform to help gauge the effectiveness of bystander CPR. Such a surrogate measure might be relevant as an efficient means to evaluate the biological comparative effectiveness of different CPR protocols.

The current investigation has limitations. As this study was observational, the association between bystander CPR and survival may still be confounded by unmeasured variables, even though we restricted the cohort to witnessed OHCA, adjusted for the spectrum of Utstein covariates, and evaluated bystander CPR stratified by TCPR and unassisted CPR. Residual confounding would also have impacted the findings of the mediation analysis, which assumed that the intervention–outcome, mediator–outcome, and intervention–outcome associations were unconfounded after adjustment for covariates. Sensitivity analysis was not performed, because the *mediation* package did not support sensitivity analysis with a logistic regression outcome model.[28] This software also did not offer the ability to perform a multiple mediator analysis that would have investigated the joint effect of all 3 waveform measures.

An additional limitation is that we were not able to measure the quality or quantity of bystander CPR, although future investigations may consider if and how conventional measures of CPR quality (ie, rate, interruptions, and depth) may be related to waveform measures. Finally, there was a period of EMS-delivered CPR between the bystander care and the sampled ECG segment because EMS rescuers provided at least 30 compressions before rhythm analysis (an "analyze early" EMS approach) under existing treatment protocols. Such a "leveler" of CPR quality before the extracted ECG segment would be expected to bias our results toward the null, suggesting that the current results may underestimate the difference in waveform measures according to bystander CPR status. We should consider these limitations in the context of the study's strengths: an investigation that addressed a gap in our understanding of bystander CPR mechanisms by combining information from a well-characterized, relatively large VF OHCA cohort with electronic defibrillator ECG data while using advanced methods to evaluate mechanism and mediation.

CONCLUSIONS

Bystander CPR, including both unassisted CPR and TCPR, correlated with more robust initial VF waveform measures, which in turn mediated up to one-half of the survival benefit associated with bystander CPR. The results provide insight into the biological mechanism of bystander CPR in VF OHCA, suggesting that much of the survival benefit conferred by bystander CPR may be a result of improvement to the myocardium as reflected by more robust waveform measures. This may provide novel considerations for how waveform measures might be incorporated to help assess the effectiveness of CPR. Future investigations might consider approaches to evaluate the quality of CPR as we strive

to leverage mechanistic understanding to improve resuscitation outcome.

ARTICLE INFORMATION

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Author contributions: Ms Bessen, Dr Coult, and Ms Blackwood were responsible for data acquisition. Drs Kwok and Coult computed the ECG waveform measures. Ms Blackwood and Dr Kwok performed the statistical analysis. All authors contributed substantially to the study design, interpretation of the results, and the drafting of the manuscript. All authors approved the submitted and final version.

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Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of study cohort and excluded cases

	Study cohort	Excluded cases	P value
Total Cases, n	1072	644	
Patient Characteristics			
Female, n (%)	225 (21)	152 (24)	0.21
Age, median (IQR)	62 (52, 72)	64 (54, 75)	0.02
Cardiac etiology, n (%)	1023 (95)	571 (89)	< 0.01
Public Location, n (%)	370 (35)	206 (32)	0.29
Bystander CPR, n (%)	814 (76)	472 (73)	0.23
Resucitation Process Variables			
EMS Response Time, min, median (IQR)	5.1 (4.0, 6.4)	5.0 (3, 6.7)	0.49
Interval between device power to ECG segment, s, median (IQR)	37 (20-60)		
Shocks delivered, median (IQR)	3 (1,6)	3 (1, 5)	0.09
Outcomes			
Sustained ROSC	799 (75)	428 (66)	< 0.01
Admit to hospital, n (%)	788 (74)	404 (63)	0.02
Survive to hospital discharge, n (%)	535 (50)	253 (39)	0.01
Neurologically intact survival (CPC 1 or 2), n (%)*	488 (46)	223 (35)	< 0.01

* Cerebral Performance Category (CPC) was missing for 5 patients in the study cohort.

Table S2. Adjusted associations between Utstein elements and VF waveform measures. VF waveform measures were log-transformed and standardized. 95% CI in parentheses.

	VF waveform measure		
Utstein element	AMSA	Peak Frequency	Median Peak Amplitude
Bystander CPR	0.40 (0.26, 0.53)	0.25 (0.11, 0.38)	0.32 (0.19, 0.46)
Female	0.13 (-0.016, 0.27)	0.24 (0.097, 0.39)	0.093 (-0.053, 0.24)
Public v. private location	0.19 (0.06, 0.31)	0.13 (0.004, 0.26)	0.16 (0.031, 0.29)
Cardiac	0.26 (-0.028, 0.54)	0.30 (-0.018, 0.59)	0.038 (-0.25, 0.32)
Age/10	-0.056 (-0.096, -0.015)	-0.063 (-0.10, -0.022)	-0.030 (-0.071, 0.012)
EMS response time	-0.034 (-0.062, -0.010)	-0.040 (-0.068, -0.012)	-0.041 (-0.070, -0.013)

AMSA = Amplitude Spectrum Area

Table S3. Adjusted and unadjusted odds ratios for predicting survival to hospital discharge with bystander CPR stratified as telephone CPR and unassisted CPR. The Utstein Model includes bystander CPR, sex, location, etiology, age, and EMS response time as predictor variables. The Mediation Models includes the Utstein variables plus a single VF measure. VF waveform measures were log-transformed and standardized. 95% CI in parentheses.

	Unadjusted	Utstein Model	Mediation Models		
			AMSA	Peak Frequency	Median Peak Amplitude
Utstein Elements					
Telephone CPR vs. no CPR	1.5 (1.1-2.1)	1.8 (1.3-2.5)	1.4 (0.98-2.0)	1.6 (1.1-2.2)	1.6 (1.1-2.2)
Unassisted CPR vs. no CPR	1.4 (1.0-1.9)	1.3 (0.89-1.8)	1.1 (0.75-1.6)	1.2 (0.82-1.7)	1.2 (0.82-1.7)
Female	1.4 (1.0-1.9)	1.4 (1.0-1.9)	1.3 (0.96-1.9)	1.2 (0.89-1.7)	1.4 (0.99-1.9)
Public v. private	1.4 (1.0-1.8)	1.2 (0.88-1.6)	1.0 (0.74-1.4)	1.1 (0.79-1.4)	1.1 (0.80-1.4)
Cardiac	1.8 (0.94-3.4)	2.8 (1.5-5.4)	2.7 (1.4-5.3)	2.5 (1.3-5.0)	2.9 (1.5-5.7)
Age/10	0.71 (0.65-0.78)	0.69 (0.62-0.75)	0.69 (0.62-0.76)	0.69 (0.62-0.76)	0.68 (0.61-0.75)
EMS response time	0.85 (0.79-0.90)	0.83 (0.78-0.89)	0.84 (0.79-0.90)	0.85 (0.79-0.90)	0.84 (0.79-0.90)
Ventricular fibrillation waveform measures					
AMSA	2.0 (1.7-2.3)		1.9 (1.7-2.2)		
Peak Frequency	2.0 (1.7-2.3)			1.8 (1.6-2.1)	
Mean Peak Amplitude	1.6 (1.4-1.8)				1.5 (1.3-1.7)

AMSA = Amplitude Spectrum Area