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Clinical paper

Emergency department point-of-care ultrasound in out-of-hospital and in-ED cardiac arrest[☆]

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ABSTRACT

Background: Point-of-care ultrasound has been suggested to improve outcomes from advanced cardiac life support (ACLS), but no large studies have explored how it should be incorporated into ACLS. Our aim was to determine whether cardiac activity on ultrasound during ACLS is associated with improved survival.
Methods: We conducted a non-randomized, prospective, protocol-driven observational study at 20 hospitals across United States and Canada. Patients presenting with out-of-hospital arrest or in-ED arrest with pulseless electrical activity or asystole were included. An ultrasound was performed at the beginning and end of ACLS. The primary outcome was survival to hospital admission. Secondary outcomes included survival to hospital discharge and return of spontaneous circulation.
Findings: 793 patients were enrolled, 208 (26.2%) survived the initial resuscitation, 114 (14.4%) survived to hospital admission, and 13 (1.6%) survived to hospital discharge. Cardiac activity on US was the variable most associated with survival at all time points. On multivariate regression modeling, cardiac activity was associated with increased survival to hospital admission (OR 3.6, 2.2–5.9) and hospital discharge (OR 5.7, 1.5–21.9). No cardiac activity on US was associated with non-survival, but 0.6% (95% CI 0.3–2.3) survived to discharge. Ultrasound identified findings that responded to non-ACLS interventions. Patients

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with pericardial effusion and pericardiocentesis demonstrated higher survival rates (15.4%) compared to all others (1.3%).

Conclusion: Cardiac activity on ultrasound was the variable most associated with survival following cardiac arrest. Ultrasound during cardiac arrest identifies interventions outside of the standard ACLS algorithm.

Introduction

Of 300,000 out-of-hospital cardiac arrests (OHCAs) annually in the United States,[1] more than 78% are transported to an emergency department (ED) for further evaluation and treatment. Less than 8% of all OHCA's survive to hospital discharge.[2] Clinical algorithms that may help guide resuscitative efforts are important. Cardiac arrests cause significant disruption to ED workflow, require significant resources and may include empiric interventions with unfavorable clinical risk-benefit outcomes.[3] Factors associated with survival include the presence of a shockable cardiac rhythm and early defibrillation, availability of by-stander cardiopulmonary resuscitation (CPR), and return of spontaneous circulation (ROSC) in the field.[2,4] The contribution of additional diagnostic modalities during ongoing resuscitation in the ED such as Point of care ultrasound[5–7] has only been evaluated in small studies.

Point-of-care ultrasound is now widely available in EDs and can provide immediate information on cardiac activity as well as potentially identifying rapidly reversible causes of cardiac arrest such as pericardial effusion or tension pneumothorax. Integrating point-of-care ultrasound into cardiac arrest protocols has been suggested,[8–10] but there have been no large studies to explore exactly how ultrasound should be utilized in Advanced Cardiac Life Support (ACLS). Several small studies suggest that lack of cardiac activity on ultrasound during cardiac arrest indicates futility.[6,7] However, these studies were underpowered, enrolled patients with shockable rhythms, and were subject to selection bias. A systematic review yielded a survival to admission rate of 2.4% in patients without cardiac activity on ultrasound.[11] Although these results seem to indicate that resuscitation in such patients may be of no clinical benefit, survival to discharge was not studied, and the studies were small and non-generalizable.

We therefore sought to determine the association between sonographically visible cardiac activity and survival for patients with pulseless electrical activity (PEA) or asystole.

Methods

Study settings

This multi-center, prospective, protocol-driven observational study involved sites across the United States and Canada. One coordinating center, six geographic regional centers and 13 local sites reporting to the regional centers were involved in the study for a total of 20 sites. Data were uploaded into a centralized database. Each site obtained approval from their respective Institutional Review Board. Consultants at Harvard University and Washington University conducted two independent ethical reviews. Feedback from these reviews was used to modify the research protocol prior to IRB approval and starting the study. This study was registered at ClinicalTrials.gov (NCT01446471).

Subject selection

Patients were included if they presented to the ED in non-traumatic cardiac arrest, were found to be in either asystole or PEA, and had ultrasound imaging performed during their resuscitation. Brief resuscitation efforts lasting less than five minutes were not included. Patients were excluded if the resuscitation was not continued after the initial ultrasound or if resuscitation efforts were halted to honor a do-not-resuscitate order.

Study protocol for resuscitation

Our research protocol required ultrasound imaging at the beginning of ACLS in the ED and a second ultrasound examination at the end of resuscitation efforts. All ultrasounds were performed during pauses in resuscitation to determine cardiac rhythm and the presence of a pulse. CPR was not halted to obtain ultrasound images. Timing of ultrasound imaging and pauses of pulse check were determined using imaging time-stamps. Physicians used sub-xyphoid or parasternal long axis views to identify cardiac activity during the resuscitation. Interpretation of ultrasound for the presence of cardiac activity was made in real time during the resuscitation. Treating physicians were unblinded to US results. There is no pre-existing standard for defining cardiac activity on ultrasound. In this study cardiac activity was defined a priori as any visible movement of the myocardium, excluding movement of blood within the cardiac chambers or isolated valve movement. Emergency physicians credentialed in bedside ultrasound by their individual hospitals performed ultrasound imaging during this study.

Adherence to the study protocol was determined using time stamps of the ultrasound imaging, which were compared with the time of ACLS. Resuscitation followed established ACLS protocols with multiple rounds of medications during CPR. Resuscitation was continued for at least one round of medications after the initial ultrasound during continuous CPR. We used a pragmatic research protocol that allowed clinician leeway as to the timing of cessation of resuscitation efforts were terminated, as there is no published guidance on when to stop ACLS.

Study outcomes

The primary outcome was the percentage of patients that survive to hospital admission. Secondary outcomes included the percentage of patients that survive to hospital discharge and ROSC. Data recorded for this study followed the Utstein nomenclature and included recommended data points with the exception of neurologic outcomes.[12] See Fig. S1.

Data collection

Study variables followed recommendations of previous cardiac arrest studies.[2,3,13,14] Data were obtained from study sheets or patient records. Ultrasound digital clips were interpreted in real-time during acquisition by physicians in the ED. Ultrasound digital clips were secondarily reviewed by a single reviewer in a blinded fashion at a later date for assessment of agreement and inter-observer agreement was evaluated using a kappa statistic. We used the suggested guidelines of Landis and Koch to describe the strength of agreement for the kappa statistic. They suggested, and we used, the following interpretation: less than 0 (poor), 0–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (almost perfect).[15]

Statistical analysis

Demographic and clinical data are presented as means with 95% confidence intervals (CI), medians with interquartile ranges, or proportions. Univariate analysis was performed with the use of Mann–Whitney *U* test for continuous variables and Fisher's exact test for dichotomous variables. Univariate analysis was first performed independently for the three outcomes of (1) survival to hospital admission (2) ROSC and (3) survival to hospital discharge. Results are provided as odds ratios (95% CI) with *p* values. Similar to prior research, variables with $p < 0.2$ from univariate analysis were included in initial multivariate modeling.[16] Collinearity was assessed between independent variables used in the multivariate analysis, and there was no considerable collinearity in any of the three models (none of the condition index was >10 from Proc Reg analysis). Interaction between independent variables was assessed in a pairwise fashion for all variables. Interaction between gender and length of resuscitation as well as gender and bystander CPR was significant ($p < 0.05$). However, the addition of interaction term did not change the direction of the main effect, and the changes occurred in odds ratio of the main effect were <10%, therefore the interaction term was not included in the final models to simplify interpretation. We used the bootstrap method to assess model overfitting. There was no considerable overfitting for any of the three models (overfitted area under the curve values were 0.6%, 1.9%, 6.7%, respectively).

Data integrity and completion was assured through communication with site directors during the study. Timing data from the out-of-hospital phase were ultimately missing in roughly 6% of cases. As noted by previous authors,[17] timing for pre-hospital events is difficult to obtain and was estimated based on a chart review when not available. In our models we adjusted for patient characteristics, elements of the cardiac arrest, therapeutic interventions during the arrest. Discrimination power of the final models was evaluated using ROC (Receiver Operating Characteristic curve). All statistical analyses were implemented with the use of SAS software version 9.4 (SAS Institute Inc., Cary NC) with the exception of model overfitting assessment, which was done in R (package rms).

Based on prior research,[4,11] we assumed an overall survival to hospital admission of 14% and a 1-to-2 ratio of patients with and without cardiac activity. A sample size of 772 patients detects an absolute increase in hospital admission of 3% from baseline for patients with cardiac activity with 80% power and a type 1 error rate of 5%.[18]

Results

A total of 953 patients were enrolled from 2011 to 2014 (Fig. 1). The number of patients demonstrating ROSC, survival to hospital admission and survival to hospital discharge was 208 (26.2%, 95%CI 23.3–29.4), 114 (14.4%, 95%CI 12.1–17.0), and 13 (1.6%, 95%CI 0.9–2.8) respectively. Overall, 263 patients (33%) had cardiac activity on the initial ultrasound in the ED. See Table 1 for patient characteristics. Cardiac activity on initial ultrasound was associated with higher ROSC and survival to hospital admission. Of the 263 patients, 134 (51.0%), 76 (28.9%) and 10 (3.8%) with cardiac activity survived to ROSC, hospital admission and hospital discharge respectively. In comparison, there were 530 patients without cardiac activity, with 76 (14.3%), 38 (7.2%), 3 patients (0.6%) surviving to ROSC, hospital admission and hospital discharge, respectively

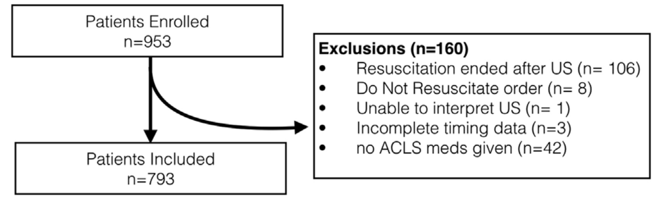

Fig. 1. Study flow diagram.

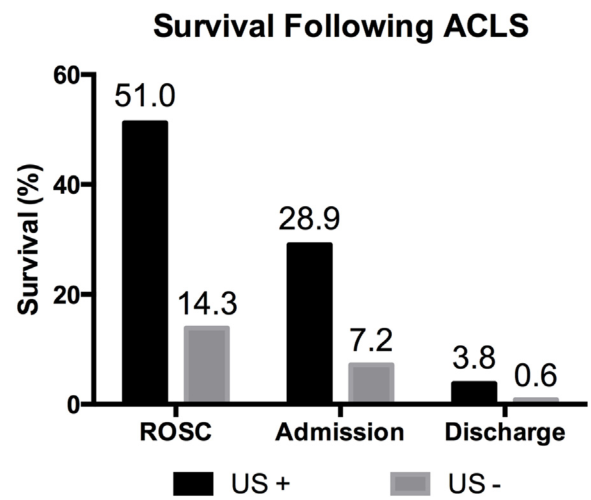

Fig. 2. Survival after cardiac arrest—black bars represent patients with cardiac activity on initial ultrasound and grey bars represent patients with no cardiac activity on initial ultrasound. Patients with cardiac activity demonstrated higher ROSC (51.2% vs 14.3, $p < 0.001$), survival to hospital admission (29.0% vs 7.2, $p < 0.001$) and survival to hospital discharge (3.8% vs 0.6, $p = 0.04$).

(Fig. 2) Agreement between initial US interpretation and review was substantial ($k = 0.63$). The number of patients with cardiac activity on the final ultrasound was similar to during the initial ultrasound (32.0% vs 33.3%), but some patients moved from no activity to positive activity (11.1%) and others moved from positive activity to no activity (11.7%).

Cardiac activity on initial ultrasound was the variable with the strongest association with survival at every endpoint. Multivariate regression analysis identified between 4 and 7 variables that were associated with survival at our various endpoints (Table 2). Ultrasound activity was associated with ROSC (OR 2.8, 1.9–4.2), survival to hospital admission (OR 3.6, 2.2–5.9), and survival to hospital discharge (OR 5.7, 1.5–21.9). All models had good discrimination (AUC 0.803, 0.762 and 0.825).

Ultrasound identified conditions that supported deviation from ACLS medication protocols. Pericardial effusion was identified in 34 patients, with attempted pericardiocentesis in 13 patients. In patients with pericardiocentesis during the resuscitation, survival to hospital discharge was 15.4%, with two patients surviving to hospital discharge. Additional patients with suspected pulmonary embolism received thrombolytics during the resuscitation, some with documented right-sided heart strain and others with visible clots in the ventricle. Two of the 15 patients receiving thrombolytics (13.3%) survived to hospital admission, and one (6.7%) survived to hospital discharge.

PEA vs asystole

The initial cardiac arrest rhythm for all patients was asystole ($n = 350$), PEA ($n = 327$) and ventricular fibrillation (Vfib) or ven-

Table 1
Patient characteristics.

Characteristic of subjects	All patients (n = 793)	Presence of cardiac activity on initial US (n = 263)	Absence of cardiac activity on initial US (n = 530)	Comparison between US activity groups
Demographics				
Age, mean (SD), years	64.2 ± 17.4	66.1 ± 16.1	63.2 ± 18.0	p = ns
Male—n (%)	492 (62.0)	151 (57.4)	341 (64.3)	p = ns
Details of cardiac arrest				
Bystander witnessed—no. (%)	334 (42.1)	141 (53.6)	193 (36.4)	p < 0.001
Bystander CPR—no. (%)	268 (33.8)	105 (39.9)	163 (30.8)	p = 0.02
Out of hospital arrest—no. (%)	680 (85.8)	197 (74.9)	483 (91.1)	p < 0.001

Table 2
Multivariate model—factors associated with survival.

	Odds ratio (95% CI)	p Value	ROC analysis
ROSC			
Gender (F vs M)	1.6 (1.1–2.3)	0.010	AUC = 0.803
Rhythm during initial US (PEA vs asystole)	2.8 (1.8–4.3)	<0.0001	(0.769–0.837)
Cardiac activity (Yes vs No)	3.0 (2.0–4.5)	<0.0001	
Length of resuscitation	1.02 (1.01–1.03)	<0.0001	
Epi per min	0.16 (0.018–1.47)	0.10	
Survival to hospital admission			
Gender (F vs M)	1.8 (1.2–2.8)	0.007	AUC = 0.762
Bystander (Yes vs No)	1.6 (1.0–2.4)	0.042	(0.710–0.813)
Rhythm during initial US (PEA vs Asystole)	2.1 (1.2–3.6)	0.011	
Cardiac activity (Yes vs No)	3.6 (2.2–5.9)	<0.0001	
Shockable rhythm (IS vs CS)	2.9 (1.4–5.9)	0.006	
Shockable rhythm (NS vs CS)	1.7 (0.97–3.1)	0.96	
Epi per min	0.12 (0.013–1.23)	0.075	
Survival to hospital discharge			
Bystander (Yes vs No)	2.6 (0.84–8.3)	0.096	AUC = 0.825
Presenting rhythm (PEA vs Asystole)	1.8 (0.34–9.3)	0.64	(0.739–0.912)
Presenting rhythm (VF/VT vs asystole)	5.5 (1.03–30.0)	0.022	
Cardiac activity (Yes vs No)	5.7 (1.5–21.9)	0.011	

tricular tachycardia (Vtach) (n = 116). This includes patients who arrested both out-of-hospital and in ED. Patients in Vfib or Vtach out-of-hospital converted to PEA or asystole during transport, so the number of patients in PEA or asystole in the ED was 414 and 379 respectively. Survival for all patients by cardiac rhythm is included in eTable 1. The percentage of patients with cardiac activity on ultrasound differed between asystolic patients (38 of 379, 10%) and patients in PEA (225 of 414, 54%), see Fig. 3.

Two variables associated with increased survival at all time points were presence of PEA and cardiac activity on initial US. The survival rate to hospital admission for patients with cardiac activity (76 of 263, 29%) was greater than patients presenting in PEA (90 of 414, 22%) p = 0.04, but no different than patients presenting with both (72 of 226, 23%) p = 0.49. Other factors such as age, presence of a shockable rhythm anytime during resuscitation, downtime prior to CPR or bystander CPR did not show a consistent association across all survival endpoints.

Lack of cardiac activity on point-of-care ultrasound and asystole in the ED was strongly associated with lack of survival at any time point. The survival rate to hospital admission for patients in asystole (24 of 379, 6.3%), patients with no cardiac activity (38 of 530, 7.2%), or both (20 of 341, 5.9%) were not significantly different (p = 0.69). Three patients with no cardiac activity survived to hospital discharge. One was a 64yo male with an out-of-hospital arrest, initially in vfib but shocked into asystole by EMS with 40 min resuscitation in the ED. The second was a 67yo male initially in vfib, defibrillated into PEA by EMS, resuscitated for 6 min in the ED. The third was a 75yo female with an out-of-hospital arrest found in asystole in her bed with unknown downtime, resuscitated for 20 min by EMS and 10 min in the ED. Although not 100% predictive, the lack of cardiac activity on ultrasound in asystolic patients in the ED demonstrated a sensitivity and PPV of 0.9 and 0.99 for non-survival to hospital discharge (see Table 3).

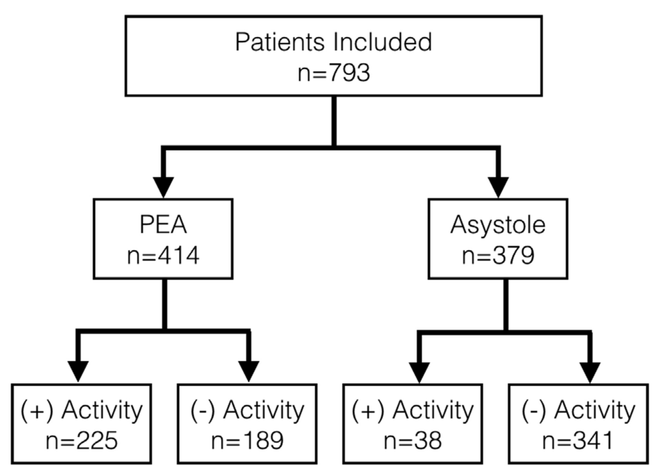

Fig. 3. Cardiac activity by initial cardiac rhythm demonstrates 45.6% of patients in PEA have no cardiac activity on ultrasound and 10% of patients in asystole have some cardiac activity on ultrasound.

Location of arrest

The patient characteristics were different for patients who arrested in the emergency department compared to those arresting out-of-hospital, but the overall survival to hospital discharge was not different. The percentage of patients with ultrasound activity was higher for patients arresting in-ED when compared to out-of-

Table 3
Sensitivity and specificity of ultrasound with no cardiac activity for non-survival.

		ROSC	Survival to hospital admission	Survival to hospital discharge
Asystole	Sensitivity	0.91 (0.90–0.93)	0.90 (0.90–0.92)	0.90 (0.90–0.90)
	Specificity	0.19 (0.09–0.32)	0.17 (0.06–0.36)	0.0 (0.0–0.8)
	PPV	0.90 (0.89–0.91)	0.94 (0.93–0.96)	0.99 (0.99–1.00)
	NPV	0.21 (0.11–0.36)	0.11 (0.04–0.23)	0.00 (0.00–0.04)
PEA	Sensitivity	0.60 (0.56–0.63)	0.53 (0.50–0.55)	0.47 (0.46–0.47)
	Specificity	0.76 (0.70–0.81)	0.80 (0.71–0.87)	0.91 (0.58–1.00)
	PPV	0.79 (0.74–0.84)	0.91 (0.86–0.94)	1.00 (0.98–1.00)
	NPV	0.56 (0.51–0.59)	0.32 (0.28–0.35)	0.04 (0.03–0.05)

hospital: 58.4% vs 29.0% ($p = 0.001$). The percentage of patients in PEA was also higher for in-ED arrests: 62.8% vs 36.8%, ($p = 0.001$). Survival to hospital admission was higher for in-ED arrests (28.9 vs 13.5, $p = 0.001$) but survival to hospital discharge was not different (3.5% vs 1.3%, p = ns). The difference in survival to hospital admission may be due more to other factors such as length of downtime rather then location of arrest, as location of arrest was not associated with survival following multivariate analysis.

Timing of events

Evaluation of timing of events during resuscitation demonstrates a few differences between patients with and without cardiac activity (Fig. S1). Differences included shorter downtime (time between arrest and CPR) and longer length of resuscitation for patients with cardiac activity with resuscitation times of 18 min (IQR 10–30) vs 12 min, (IQR 8–17), $p < 0.05$. Other measures of resuscitation effort such as time between doses of epinephrine and pauses for pulse checks were similar. Patients with and without cardiac activity had epinephrine every 5.55 min (IQR 4.55–9.44) and 5.55 min (IQR 4.00–8.33). The average time spent recording ultrasound images during pulse checks was also not different (4.9 s vs 4.4 s, $p > 0.05$).

Discussion

Our study of patients in cardiac arrest demonstrates that the presence of cardiac activity on the initial ultrasound during resuscitation is the variable most associated with survival following cardiac arrest. This is the first large, multi-center study exploring the use of ultrasound during ACLS, validating observations made in smaller studies.[5–7,19–22] Rates of ROSC in previously published studies for patients in cardiac arrest with cardiac activity range from 24% to 73%. Our study found a ROSC rate of over 50% if cardiac activity was detected vs 14.1% if none was documented. Other features such as bystander CPR identified by previously studies[16,23] were less strongly associated with survival. The overall survival rate to hospital discharge in patients with cardiac activity on ultrasound was 3.8%, which is higher then other large out-of-hospital arrest studies (1.4% and 2.7%).[4,24] Those publications consist of resuscitation efforts without ultrasound, and we speculate that the increase in survival can be at least partially explained by cases where ultrasound identified non-ACLS interventions (i.e., pericardiocentesis, thrombolysis). It is also possible that the better outcome reported in patients with cardiac activity on ultrasound was related to prolonged resuscitation efforts. This is unlikely to be the primary cause of increased survival, as multivariate modeling found no association between length of resuscitation and increased survival. In addition, no prior research supports an association between longer resuscitation efforts and survival in out-of-hospital arrest, and studies on in-hospital arrests have been mixed.[25,26]

The overall survival rate to hospital discharge in this study was relatively low at 1.6% and included patients arresting out of hospital as well as patients arresting in the emergency department. Previously published survival rates for out-of-hospital arrest were comparable to our study (1.4% and 2.7%).[4,24] Other studies on emergency department cardiac arrest demonstrate higher survival rates (22.2%).[27] Our survival rate is lower when compared to previously published in-ED arrests for a number of reasons. First, our data includes out-of-hospital arrests and not just in-ED arrests. Second, patients arresting in the emergency department who were rapidly resuscitated were not included in the current study. These patients were successfully resuscitated before an ultrasound could be performed. Finally, it is also possible that an element of selection bias is contributing to the relatively lower survival rate.

Ultrasound identified a group of patients who are treated outside of the current ACLS medication algorithm (pericardial effusion, signs of pulmonary embolism). Overall, 34 of 793 patients had a pericardial effusion, with 13 pericardiocentesis procedures. This small group of patients demonstrated a survival rate to hospital discharge (15.4%) significantly higher than in all other patients in our study (1.3%). Additional patients had findings of possible pulmonary embolism such as right heart strain but the benefit in this group was not as great (6.7% survival to hospital discharge). The identification of findings that support interventions outside of ACLS medications and the increased survival in this subgroup illustrates the utility of integrating ultrasound into standard ACLS algorithm. The utility of ultrasound during ACLS is also demonstrated by the finding that roughly 10% of patients in asystole demonstrated cardiac activity on ultrasound, a finding that has been seen in other smaller studies.[5,20,21,28] Prior studies describing asystolic patients with sonographic cardiac activity did so with an overall lower prevalence (0.7–5%) but it is possible that in unblinded studies the rhythm interpretation and ultrasound interpretation influence each other. The blinded review of ultrasound images in the current study supports the lack of ultrasound activity in patients considered in asystole on the monitor.

Our study also demonstrates a strong association between lack of cardiac activity and non-survival. This study is not the first to find this association, but prior publications suffered from methodological flaws. A meta-analysis of 11 studies using echocardiography in cardiac arrest found no cardiac activity is strongly associated with lack of ROSC, but these studies included traumatic cardiac arrests and a primary outcome of ROSC rather than survival to hospital discharge. In that meta-analysis, only 2.4% of patients without cardiac activity developed ROSC (compared to 14.5% in our current study).[11] It has been noted that physicians feel more comfortable ceasing resuscitative efforts if ultrasound shows no cardiac activity.[7] It is possible that this comfort may be resulting in under-resuscitation of patients in cardiac arrest and this contributed to a selection bias with a lower ROSC in prior studies.

Ultrasound has been proposed to help decrease ACLS interventions in patients where survival is thought to be exceedingly small.

It has been suggested that resuscitative efforts can be terminated if a patient in cardiac arrest has no cardiac activity on ultrasound.[29] In our study, the lack of cardiac activity at the beginning of resuscitation was strongly associated with non-survival, but three of these patients survived to hospital discharge. Subgroup analysis demonstrates that the lack of cardiac activity and asystole together are more associated with non-survival. This may be a population where prolonged resuscitation may not provide measurable benefits.

In summary, point-of-care ultrasound demonstrated a valuable potential role in resuscitation following cardiac arrest by identifying patients with higher likelihood of survival as well as patients who benefit from interventions outside of strict ACLS protocol (pericardiocentesis for pericardial effusion or thrombolytics for possible pulmonary embolism). Ultrasound may also identify patients where prolonged resuscitation may not provide measurable benefit (asystolic patients without cardiac activity).

Limitations

The most significant limitation of this study involved the potential of bias related to the lack of blinding of the ultrasound results. The clinicians were unblinded to the ultrasound results and patients with cardiac activity on ultrasound demonstrated longer resuscitation times. To decrease potential bias related to clinician opinion of the ultrasound results, we excluded patients with short unsuccessful resuscitations (under 5 min) to avoid patients with resuscitation efforts stopped because of a negative ultrasound. Other metrics of resuscitation effort such as timing of epinephrine and length of resuscitation pauses during ultrasound imaging were similar for patients with and without cardiac activity. It is possible that bias contributed to decreased resuscitation times in patients without cardiac activity, but the decision to not blind clinicians to the ultrasound results was following the ethical review during the research protocol development.

Another limitation of this study is that survival outcomes did not include neurocognitive testing. We were unable to include this outcome because of resource constraints, which limits any conclusions regarding neurologically intact survival. Our study did also not include a research protocol detailing all aspects of the resuscitation effort. Clinicians were able to choose medication timing and overall length of resuscitation, which may result in unmeasured differences between groups. Finally, it is possible that there was a selection bias in patients actually enrolled in the study, as evidenced by the overall enrollment rate for sites involved in this study.

Conflict of interest statement

Dr. Romolo Gaspari has no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.09.018.

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