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Effect of Prehospital Echocardiography in Cardiac Arrest to Augment Chest Compression Positioning

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EFFECT OF PREHOSPITAL ECHOCARDIOGRAPHY IN CARDIAC ARREST TO
AUGMENT CHEST COMPRESSION POSITIONING

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<u>Abstract</u>

Cardiac arrest, characterized by the loss of mechanical activity of the heart, is a life-threatening medical condition that is almost always fatal if not treated immediately. The protocols for cardiopulmonary resuscitation used by emergency medical personnel during out-of-hospital cardiac arrests do not account for cardiac and thoracic anatomic variation when positioning chest compressions. This study will examine whether evaluating chest compression efficacy using transthoracic echocardiography in the prehospital setting will increase the rates of survival to hospital admission in adults suffering atraumatic out-of-hospital cardiac arrest. We will recruit paramedics from four emergency medical services agencies to participate in a prospective crossover study and be trained in basic echocardiography to be used in the field. The results of this study may support imaging in out-of-hospital settings to promote more effective cardiopulmonary resuscitation, increasing rates of survival for patients suffering cardiac arrest.

Chapter 1: Introduction

1.1 Background

Cardiac arrest is a deadly condition defined as the loss of mechanical activity of the heart confirmed by the absence of signs of circulation.[1] Over 350,000 people are treated annually for cardiac arrests that occur out-of-hospital.[1] Unfortunately, survival rates for out-of-hospital cardiac arrests (OHCA) are quite low; only about 7.6% of adults sustaining cardiac arrest outside of a hospital survive to be discharged from the hospital.[2] Survivability of an OHCA varies widely depending on several factors, including bystander cardiopulmonary resuscitation (CPR), availability and early use of an automated external defibrillator (AED), and type of electrical rhythm present during cardiac arrest.[2] The timely application of high-quality chest compressions as part of CPR has been proven to increase the likelihood of survival. Rapid and effective CPR may be one of the reasons that in-hospital cardiac arrest survival rates are as high as 50%, which is considerably higher than that of OHCAs.[3] Patients who suffer cardiac arrest outside of the hospital have low odds of survival unless the cardiac arrest is witnessed, CPR is initiated quickly and performed effectively, and emergency medical services (EMS) are activated promptly to ensure early defibrillation and advanced cardiac life support (ACLS). The survivability of OHCA remains quite low, even in best case scenarios. Due to the relatively small window of time in which a patient suffering an OHCA can survive, many of the interventions aimed at improving survival rates have been incorporated by EMS employees, specifically emergency medical technicians (EMTs) and paramedics.

One of the newest diagnostic tools to be introduced in the prehospital setting is the portable ultrasound device. Lightweight and low-cost, these devices are easily integrated into the prehospital assessment and even during resuscitation. Several studies examining the feasibility of prehospital ultrasound use have proven that paramedics can be trained in basic echocardiography in a short period of time and apply these skills to obtain high-quality images in the prehospital environment.[4-6] Several prospective observational studies have also been performed to determine the effect of paramedic-guided echocardiography during cardiac arrest.[7,8] Unfortunately, there are currently no published randomized controlled studies that examine the effect of prehospital echocardiography on patient outcomes, such as survival, in atraumatic cardiac arrest.[9]

1.2 Statement of the Problem

OHCA survival rates in non-traumatic adult arrests are only approximately 7.6% nationwide[2]. In New Haven, the most recent data on survival show that 9.2% of patients suffering non-traumatic cardiac arrest survive to discharge, and 11.2% survive to hospital admission.[10] Cardiac arrest survival increases with timely and effective CPR. There are currently no imaging modalities widely available to prehospital clinicians to determine whether CPR is being performed effectively in cardiac arrest.

In a recent Yale hypothesis-generating series of five patient cases, it was found that unique patient anatomy limited the effectiveness of resuscitation with either manual or automatic chest compression devices that did not directly cause compression of the left ventricle, though properly positioned according to standard protocol.[11] Focused transthoracic echocardiography in the emergency department using parasternal long axis and subxiphoid views showed that positioning of chest compressions in the standard

location compressed structures that were sub-optimal, such as the aorta and right heart.[11] Swine models have shown that optimal hemodynamic parameters are achieved when the left ventricle of the heart is directly compressed during CPR, thus enhancing the likelihood of return of spontaneous circulation (ROSC).[12] In the five cases published by Dr. Liu et al., repositioning of chest compressions directly over the left ventricle using visual information gathered from the echocardiogram resulted in ROSC in four patients, and determined an etiology for the abrupt cardiac arrest in the fifth patient. Unfortunately, in all five cases spontaneous circulation either could not be maintained for a sufficient period of time, or the patient suffered significant neurological compromise due to prolonged inadequate efforts at resuscitation.[11] Currently, there have not been any randomized studies performed on the efficacy of CPR positioning using focused transthoracic echocardiography, either in the hospital or in the prehospital setting. In summary, standard CPR positioning does not take natural anatomical variation in patients into account; without an imaging modality to ascertain whether the correct anatomy is being compressed, these patients have a very small likelihood of survival.

1.3 Goals and Objectives

EMS personnel provide rapid care to patients suffering OHCA. The rapid initiation of uninterrupted effective CPR has been proven to improve likelihood of patient survival in OHCA. By teaching paramedics to perform a basic echocardiographic assessment using a portable ultrasound device, they can quickly assess whether the left ventricle of the heart is being compressed effectively by the person or device performing CPR without interrupting compressions. Effective compression of the left ventricle increases the

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likelihood of return of spontaneous circulation and hemodynamic stability, thus increasing the likelihood of survival to hospital admission.

1.4 Hypothesis

We hypothesize that paramedic-performed focused transthoracic echocardiography in cardiac arrest to determine accuracy of chest compression placement during CPR will result in higher rates of survival to hospital admission when compared to standard care as per statewide EMS protocols.

1.5 Definitions

Prehospital - occurring before or during transportation to a hospital

Out-of-hospital cardiac arrest (OHCA) - the loss of functional cardiac mechanical activity in association with an absence of systemic circulation, occurring outside of a hospital setting.[13]

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Chapter 2: Review of the Literature

2.1 Introduction

A systematic literature search was performed using multiple databases, including Ovid (Medline), EMBASE, Scopus, Cochrane Medical Library, and Pubmed. The literature search was performed between December 2019 and January 2020 using the following terminology. Key terms used to search databases with respect to cardiac arrest included *out-of-hospital cardiac arrest, OHCA, heart arrest, cardiac arrest, cardiopulmonary resuscitation*, and *CPR*. Terms regarding imaging included *ultrasonography, ultrasound, POCUS, FEEL, echocardiography, echocardiogram, echo*, and *transthoracic echocardiography*. Key terms regarding the setting of the intervention included *emergency medical services, EMS, paramedic, emergency medicine, emergency medical technician, prehospital*, *pre-hospital,* and *out-of-hospital*. Key terms used to search for specific protocol parameters included *crossover study design, cross-over*, and *cross over*. Furthermore, searches were performed for the specific outcome being studied, including *survival, survival to admission,* and *survival to hospital admission.* The search was limited to adult population (ages 18 and older), articles published within the last ten years, and articles in English. Article abstracts were subsequently screened for relevance.

2.2 Overview of the Burden of Out-Of-Hospital Cardiac Arrest

OHCA is frequently encountered and treated by emergency medical personnel in the United States. 2019 estimates from the American Heart Association state that the annual incidence of EMS-assessed OHCA in adults in the United States is 356,461 (95% CI = 350,349-362,252).[1] National estimates of survival to hospital discharge in 2017

from the Cardiac Arrest Registry to Enhance Survival (CARES) database were a dismal 10.4% among adults.[2] Conversely, the in-hospital cardiac arrest rate of survival to discharge is 25.6% (based on data from 311 US hospitals)[3]. There are large regional variations in OHCA survival to hospital discharge, ranging from 3.4% to 22.0% (median odds ratio = 1.40, 95% CI = 1.32-1.46).[4] Based on 2018 calculations from the CARES database, the national rate of survival to hospital admission following OHCA was 28.2%.[2] These data indicate that there is room for improvement in the treatment of OHCA, and that perhaps it is possible to increase patient survival rates.

Survivors of cardiac arrest also suffer from many functional impairments that ultimately reduce their quality of life.[5,6] Among the sequelae reported one year post-event by 141 patients in a cohort that survived cardiac arrest, 13% displayed severe cognitive deficits, 15% reported anxiety and depression, 28% displayed symptoms of posttraumatic stress disorder (PTSD), and 52% complained of severe fatigue.[7] This study demonstrates that survival of cardiac arrest is not without long-term consequences that affect quality of life.

2.3 Overview of Ultrasonography in the Prehospital Setting

As point-of-care ultrasound (POCUS) becomes more ubiquitous in both the emergency department and in prehospital settings, clinicians have found new ways to incorporate these devices into patient assessments to change the course of treatment. The utility of prehospital POCUS has been most critically evaluated in the diagnosis and treatment of cardiac arrest, trauma, and dyspnea.[8] The findings regarding POCUS use in the setting of cardiac arrest will be discussed below in the next section. A recent systematic review detailed the findings of several studies that found utility in POCUS for

trauma patients.[8] A prospective trial by Press et al. found that the specificities for helicopter-based emergency medical personnel to identify hemoperitoneum and pneumothorax using POCUS examination were 94.1% (95% CI = 89.2%-97%) and 99.5% (95% CI = 98.2%-99.9%), respectively.[9] Sensitivities, on the other hand, were just 46% (95% CI = 27.1%-94.1%) and 18.7% (95% CI 8.9%-33.9%), respectively.[9] These data suggest that the helicopter-based emergency medical personnel participating in this study were very good at identifying disease-free anatomy, but were much less accurate at identifying pathological states. Another study found that identification of pneumothorax by non-physician air medical personnel using prehospital POCUS had an overall accuracy of 91% (95% CI = 85-95%) when compared to chest computed tomography, with a specificity of 96% (95% CI = 90-98%) and a sensitivity of 68% (95% CI = 46-85%).[10] Once again, these data suggest that while prehospital clinicians are able to adequately view normal anatomy on ultrasound, they struggle with identifying pathology. Further training may be required to focus on the presentation of pathology in future trials. Furthermore, the prehospital clinicians who participated in the study were composed of flight nurses and paramedics, with a mean of 10.6 years of experience in air medical services.[10] The level of experience may dictate the skill with which these clinicians are able to use POCUS. Additionally, flight nurses have different educational backgrounds and a slightly different scope of practice than paramedics, and thus different strengths and weaknesses.

POCUS has also been used in the evaluation of dyspnea, especially in patients with multiple comorbidities. In patients with dyspnea, POCUS can be used to distinguish dyspnea caused by congestive heart failure (CHF) from dyspnea caused by chronic

obstructive pulmonary disease (COPD).[11] This study by Neesse et al. determined that

POCUS-elicited pleural effusion was demonstrated in 100% of patients with dyspnea

caused by CHF, whereas it was only seen on 20% (p<0.01) of ultrasound recordings

performed in patients having COPD exacerbations, thus allowing emergency medical

clinicians to correlate other clinical findings to narrow their differential diagnosis.[11] In

the prehospital setting, there are limited modalities available to discern causes of

dyspnea. Tools that are frequently used in the hospital, such as arterial blood gases and

chest x-rays, are simply not available in prehospital medicine. With only a few tools

(such as physical exam, capnography, and pulse oximetry) at their disposal, paramedics

in prehospital settings cannot easily discern the etiology of dyspnea and may be inclined

to withhold or delay interventions such as fluid resuscitation, for fear of exacerbating the

symptoms. The use of POCUS in this setting may provide prehospital clinicians with the

opportunity to narrow a broad differential diagnosis and deliver appropriate interventions.

2.4 Use of Echocardiography in Cardiac Arrest

Portable ultrasound devices have become increasingly prevalent in the prehospital

setting due to their relatively low cost, durability, and portability.[12] Additionally, portable

ultrasound devices are accurate. One study by Vourvouri et al. showed 100% (kappa =

0.969) agreement with standard echocardiographic findings using portable ultrasound

devices for effusion, and 93% (kappa = 0.871) agreement for left ventricle function and

wall motion abnormalities.[13] These data suggest that the portable ultrasound device is an

effective substitute for traditional echocardiographic equipment when the latter is

unavailable. Another study by Rugolotto et al. found a sensitivity of 97% and a

specificity of 99% for echocardiographic evaluation of moderate to severe anatomic pathology using a portable ultrasound device.[14]

There have been several influential studies performed to investigate the effects of using ultrasonography in cardiac arrest on various outcomes, such as effect on treatment decision and correlation of cardiac movement with survival.[15,16] Unfortunately, there have been no randomized, controlled studies to date that compare survival in groups receiving prehospital echocardiography for OHCA to controls. A selection of prospective observational studies has formed the basis of our understanding of prehospital echocardiography thus far. In a study of 42 patients, Aichinger et al. found that the use of echocardiography in non-traumatic OHCA to view cardiac movement (versus cardiac standstill) predicted survival with a 97.1% positive predictive value.[17] This study found that of the 32 patients who had complete cardiac standstill on the echocardiographic assessment during resuscitation, only one (3.1%) survived to hospital admission, whereas four out of the ten patients (40%) with cardiac movement on the assessment survived to hospital admission (p=0.008).[17] This suggests that echocardiography can be used to evaluate cardiac motion to predict prognosis in cardiac arrest patients. Using this information, clinicians can use echocardiography to confirm lack of cardiac motion in cases where termination of resuscitative efforts may be questionable. Many emergency physicians now use bedside echocardiography as a means to support the decision to terminate resuscitation.[18] An observational study by Breitkreutz et al. in the prehospital setting used a similar type of echocardiographic assessment to view cardiac motion.[19] The authors found that the FEEL (focused echocardiographic evaluation in life support) assessment was useful in differentiating between true cardiac arrest and profoundly low

cardiac output, a distinction that can significantly alter patient management.[19] Although ACLS protocols dictate that a clinician should seek to find a cause of etiology of cardiac arrest, there are no specific guidelines that address how to do so.[20] Breitkreutz et al. found that echocardiographic findings from the FEEL assessment resulted in a warranted change in patient management 89% of the time.[19] Peri-resuscitative echocardiography in the hands of prehospital clinicians can provide a tool to determine the etiology of a cardiac arrest, when no clear etiology is found with traditionally available tools. The FEEL assessment can reveal conditions such as tamponade, profound hypovolemia, and myocardial insufficiency as causes for abrupt cardiac arrest.[19] Breitkreutz et al. found that introducing this peri-resuscitative echocardiographic assessment had potential to be useful in the prehospital setting, but had thus far mainly been taught to physicians in acute care specialties.[19] Further implementation in the prehospital setting may be useful, but remains unproven given that no randomized trials using ultrasound technology and its effect on survival currently exist. The study by Breitkreutz et al. was not randomized and was limited by the fact that it did not independently review all images gathered due to technical limitations. Furthermore, the study was conducted in Germany and employed emergency physicians to perform the peri-resuscitative echocardiographic assessment. Due to the much smaller number of emergency physicians practicing prehospital medicine in the United States (when compared to paramedics and EMTs), it is difficult to generalize these results to an American paramedic-based prehospital medicine system.

Based on the findings of Breitkreutz et al., a similar study set in a Dutch helicopter emergency medical service enrolling 56 patients recently found that a prehospital echocardiographic assessment resulted in treatment changes in 88% of

cardiac arrests.[16] In 32 patients, the ultrasound findings supported the termination of resuscitation.[16] In 21 patients, the ultrasound findings supported the continuation of resuscitation efforts.[16] This study was also key in elucidating some of the limitations of introducing a peri-resuscitative intervention in a high stress environment. It was found that a high number of case report forms, designed to record information about time of cardiac arrest, start of basic life support (BLS), initial observed heart rhythm, timing of ROSC or termination of resuscitation, were not filled out by the emergency physicians staffing the EMS service. The speculated reasons for this lack of data were "nonadherence to the protocol, a lack of time due to subsequent missions, or plain forgetfulness," as well as "dismissal of the entire procedure due to poor image quality, or the impression the scan contributed nothing to patient management," thus introducing selection bias.[16] Unfortunately, this suggests that such limitations may occur in other studies that take place in the prehospital setting treating cardiac arrest if proper adherence protocols are not implemented.

Portable echocardiography may also be useful in dictating the direction of patient management beyond just the continuation or termination of resuscitative efforts. In a retrospective analysis of the REASON study, Gaspari et al. implemented a bedside echocardiographic assessment in patients in PEA (pulseless electrical activity) arrest. Their findings helped identify a subset of patients with organized cardiac activity who responded well to continuous adrenergic agents, resulting in higher rates of survival to hospital admission.[21] Although this study was not randomized and included patients suffering cardiac arrest in the emergency department, as well as out-of-hospital, it is one of the few studies available that examines how using echocardiography during cardiac

arrest to determine treatment plans based on cardiac activity affected survival to hospital

admission. Patients with organized cardiac activity (as seen on echocardiography) treated

with epinephrine had a survival to hospital admission rate of 37.7%, compared to 45.5%

for patients with organized rhythms treated with standard ACLS (p<0.005).[21] Patients

with disorganized activity treated with standard ACLS interventions demonstrated a rate

of survival to hospital admission of 17.9%, compared to 0% for patients with

disorganized activity receiving epinephrine (p<0.005).[21] Although this trial did not

directly study the relationship between peri-resuscitative echocardiography and survival

to hospital admission, it did use echocardiography as a tool to view cardiac activity, and

determined that this procedure may have beneficial effects on survival.

2.5 Feasibility of Implementing Paramedic-Guided Echocardiography in a Prehospital Environment

Determining whether prehospital clinicians can successfully be taught to perform

the assessment must be carefully considered as one of the challenges associated with

implementing a new assessment in the prehospital setting. Several studies examining the

effectiveness of echocardiography in the prehospital setting employed emergency

physicians to perform the echocardiographic assessment.[19,22] This has both advantages

and disadvantages. Most emergency physicians are already competent in emergency

ultrasound and echocardiography, and only need a minimal amount of supplemental

training to implement this intervention in the prehospital setting.[23] For example,

emergency physicians employing point-of-care echocardiography in an ICU setting were

able to obtain adequate images in 100% of the 151 enrolled patients.[24] In most European

countries, emergency physicians are employed to deliver the bulk of prehospital care

under the Franco-German model of EMS delivery.[25] However, in the United States,

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emergency physicians who practice prehospital care are relatively uncommon.[25] Instead, paramedics and EMTs make up the majority of clinicians who deliver prehospital care.

It would be very difficult to conduct an adequately powered study with a sufficiently large sample size using only emergency physicians to perform prehospital interventions. Fortunately, in acknowledgement of this limitation, several studies have also examined the feasibility of educating paramedics to successfully perform echocardiographic assessments. Chin et al. found that 75% of paramedics were able to identify at least one ventricle on echocardiographic assessment after a short 2 hour training course, but recommended further training.[26] Heegaard et al. implemented a six-hour long training course for paramedics (including three hours of practical training and additional one hour of refresher training) in Focused Assessment Sonography in Trauma (FAST) and abdominal aortic exams.[27] The authors found that paramedics were able to obtain adequate images in 92% of patients receiving the FAST exam (which includes a cardiac exam component), as verified by experienced sonographers.[27] The PUCA (Paramedic Ultrasound in Cardiac Arrest) study, published in 2017 by Reed et al., set out not only to determine whether paramedics could be trained to perform and interpret echocardiography while delivering life support, but whether they could perform the echocardiographic assessment during a short pulse-check window, and whether this intervention affected the quality of cardiac arrest care.[28] The training period for paramedics in this trial consisted of a two-hour lecture alongside four hours of practical sessions and simulations. The study found that paramedics obtained an adequate view of the heart 80% of the time on the first try and 100% of the time on the subsequent attempt.[28] These views were deemed excellent/good or satisfactory 68% of the time on

the first try.[28] However, a view was only obtained within the 10-second pulse check

timeframe approximately 44% of the time.[28] The study also found that performing the

echocardiographic assessment prolonged hands-off time during CPR to 17 seconds,

which is unacceptable per ACLS guidelines.[20] It was determined that while paramedics

could feasibly be taught to perform adequate echocardiographic assessments during life

support with satisfactory views, this intervention also delayed life-saving care in some

cases.[28] Fortunately, it is less likely that this issue will arise in our proposed trial because

paramedics will be instructed to perform the echocardiographic assessment while CPR is

ongoing, thus removing the need to perform the assessment during the short pause in

compressions.

2.6 Review of Confounding Variables

There are many potential confounding factors to consider when studying the

effect of an intervention in cardiac arrest on survival. Due to the unpredictable and

demanding nature of delivering life support outside of a hospital with limited available

tools, many factors may affect patient outcomes, including survival. Certain aspects of

the EMS system itself create unexpected effects on patient outcomes. For example, many

ambulance services, including those that are to be included in this trial, have crews of two

individuals that respond to 9-1-1 calls. Due to the demanding nature of caring for a

patient in cardiac arrest, it is often the case that a second crew of two individuals will

respond to the same call to provide necessary assistance. However, this may not always

be possible depending on the call volume or staffing available at that point in time. In a

study where one paramedic is designated to obtain an echocardiographic assessment

during cardiac arrest, it may be possible that more crew members are required to deliver

adequate care to the patient. In this case, a crew of four members will almost inevitably deliver better care than a crew of two, and this may affect the patient's survival. A study by Sondheim et al. investigated the optimal number of crew members needed to collect sufficient data from a new smartphone application designed to assist EMS personnel in recording the timing of interventions performed.[29] Using simulations, it was found that as crew sizes increased from three to four members, totals delays in care time decreased from 13.43 to 2.13 seconds (p<0.001).[29] Similarly, increasing group size correlated to an increase in the number of interventions recorded in the application (p=0.009).[29] The greatest improvements were seen between groups of three to groups of four. It was determined that the application should not be used in groups of less than four due to the increased likelihood of insufficient entries recorded and delays in care time. The application from this study demonstrates that introducing a novel intervention in a prehospital setting may add to the demand that EMS clinicians experience when delivering care in the field. As the number of crew members increases, tasks can be delegated and shared to ensure that patient care is not compromised. In our study, it will be necessary to ensure that all paramedics responding to cardiac arrest calls are able to work with an appropriate number of team members to ensure proper patient care delivery.

The level of experience of the paramedic performing the intervention is another variable that may have a confounding effect on both willingness and ability to use transthoracic echocardiography, as well as survival outcomes. A study of ambulance crews' length of experience and its effect on patient survival by Soo et al. found that patients' chances of survival increased once EMTs had 4 or more years of experience (odds ratio 2.71, 95% CI 1.17-6.32, p=0.02) when compared to EMTs with less than a

year of experience.[30] Additionally, patients' chances of survival increased when

paramedics had just one or more years of experience (odds ratio 2.68, 95% CI 1.05-

6.82, p=0.04) when compared to paramedics with less than a year of experience.[30]

However, a more thorough systematic review by Dyson et al. found that there was no

clear evidence that EMS practitioner career experience or exposure to OHCA was

associated with survival rates.[31] This was due largely in part to the limitations of the

studies reviewed, which included a lack of controlling for confounding. Although data on

whether clinician experience affects survival outcomes is inconclusive, this is a

confounder that should be controlled for during the final data analysis portion of the

study.

Studies have also shown that rates of survival in cardiac arrest are statistically

different based on race and socioeconomic status. In a study of 4053 cardiac arrests in

New York City, it was found that age-adjusted survival to hospital admission was

significantly higher in Caucasians (11.3%) when compared to African-Americans (6.0%,

p<0.01). Similarly, Caucasians also had a higher survival to hospital admission rate

when compared to Hispanics (8.6%, p<0.01).[32] OHCA also occurs much more frequently

in poorer populations; OHCA rates were found to be nearly double (incidence rate ratio

1.9, 95% CI = 1.8-2.0) in census tracts from the lowest socioeconomic quartile when

compared to the highest socioeconomic quartile.[33] According to data from the CARES

database, men are more likely to suffer non-traumatic OHCAs, composing 62.1% of

OHCA patients treated by EMS in 2018.[34] Conversely, women made up just 32.9% of

OHCA patients.

Comorbidities are another factor that has strong influence over survival from cardiac arrest. In particular, obesity is likely to be a confounding variable as it not only has an effect on survival, but also presents a challenge for clinicians attempting to obtain images on echocardiography due to body habitus. In a prospective cohort of 81,722 women, BMI of 21.0-24.9 was associated with a decreased risk of sudden cardiac death (RR=0.27) when compared to individuals with a BMI >35 (RR=1 p<0.01).[35] Another comorbidity that is common in those suffering OHCA is atherosclerosis. In a large study of 1,274 patients occurring over the course of 10 years, patients suffering OHCA were subjected to imaging (CT scan or coronary angiography) in the hospital.[36] It was found that 61% of patients who had suffered OHCA had at least one significant coronary lesion that was thought to have contributed to cardiac arrest.[36]

Despite the wide variety of confounding variables associated with studies set in a prehospital setting, the influence of these variables will be minimal due to the crossover design of this trial. Participants will be matched, thus minimizing the effect of demographic and comorbid condition confounding. Many trials with a crossover design have a carryover effect inherent to the design of the trial that may act as a confounding variable. Fortunately, the intervention used in our trial will not have this effect because echocardiography will not have any lasting effects on the individual. Therefore, it will not be necessary to incorporate a wash-out period in the study design.

2.7 Review of Relevant Methodology

The following sections will include reviews of methodology used in other prominent trials relevant to the intervention and outcomes of our proposed study.

2.7.1 Selection of Intervention

As discussed in previous sections, the use of portable ultrasound devices in the prehospital setting has been of great interest to many researchers. The advent of portable, affordable, and durable imaging has created an opportunity to implement a new imaging tool earlier in the patient care process, prior to initiation of care in the emergency department. As previously discussed, portable ultrasound has been amply studied in the applications of cardiac arrest, trauma, and dyspnea.[8] One study in particular found a relatively novel use for portable ultrasound that seemed potentially applicable to the prehospital setting. In a study of five patient cases in 2019, Liu et al. used portable ultrasound devices to perform a very simple echocardiographic assessment of the heart while chest compressions were performed, to determine whether the left ventricle was adequately compressed.[37] This study had several limitations, not least of which was its strictly observational nature and small sample size of five patients. No conclusions about patient outcomes could realistically be drawn from this small cohort. However, this study did introduce an echocardiographic assessment that could be performed in the peri-resuscitative state without the need for pausing chest compressions. A previous study by Reed et al. implementing an echocardiographic assessment during cardiac arrest found that the addition of this new intervention during the 10 second "pulse check" window resulted in longer pauses in CPR, which was deemed unacceptable.[28] However, the assessment proposed by Liu et al. does not require a pause in compressions, mitigating the risk of delay in patient care.[37] Additionally, the assessment proposed by Liu et al. was relatively simple; it involved the use of modified parasternal long axis, apical four-chamber, and subxiphoid views to view the heart while compressions were in progress.

Given the feasibility of teaching prehospital clinicians to perform similar assessments, it appeared likely that prehospital clinicians could also learn to obtain the described views with CPR in progress.[26-28]

2.7.2 Review of Study Design, Primary Outcomes, and Secondary Outcomes

The choice to perform a prospective randomized crossover study stemmed from the use of crossover designs in other studies employing emergency medical personnel in OHCA. A 2015 study by Nichol et al. enrolled patients suffering OHCAs into a trial studying the effect of continuous versus interrupted chest compressions on survival to hospital discharge.[38] This study was implemented within the network of clinical sites of the Resuscitation Outcomes Consortium, which included 114 EMS agencies across North America. This expansive study allowed for a very large sample size, and the crossover design minimized the effect of confounding variables due to matching. Of note, the authors stated that some between-group differences were found in the characteristics of patients, but these differences were attenuated through post hoc adjustment. As is proposed in our study, randomization occurred at the institutional level, with EMS agencies being assigned to individual randomization clusters. The primary outcome in this study was rate of survival to hospital discharge, with secondary outcomes including rates of transport to hospital, ROSC at ED arrival, admission to hospital, survival to 24 hours, days of hospital-free survival, discharge home, and neurological function based on modified Rankin scale.[38] Many of the outcomes studied in this trial are also proposed in our study due to similarities in the population (patients suffering OHCA).

Another strong study published by Hallstrom et al. examined the effect of manual versus mechanical chest compressions on survival to four hours after the 9-1-1 call.[39]

Although this older study was published in 2006, it remains one of the few randomized controlled studies that examines the effect of a peri-resuscitative intervention on survival. Much like the trial published by Nichol et al., this study employs EMS personnel to implement an intervention in patients suffering OHCA and uses a cluster-randomized crossover design. The authors cite the "cost and inconvenience" of moving and carrying the mechanical chest compression device as one of the primary reasons for the crossover design.[39] Similar to our proposed study, the crossover design allows researchers to purchase half the amount of equipment needed for the intervention, since groups in the clusters will switch protocols every specified time period. Furthermore, the cluster randomization technique ensures that equipment can be swapped every few weeks or months, rather than at every 9-1-1 response. The primary outcome in the Hallstrom study was rate of survival to four hours after the 9-1-1 call, with secondary outcomes including rates of survival to hospital discharge and neurologic function using a cerebral performance score.[39] Because survival to hospital discharge tends to be so rare, the primary end point we have proposed in our study is survival to hospital admission. This outcome is quite similar to the primary outcome in the study by Hallstrom et al., because most patients who survive an OHCA in the emergency department will likely be admitted to the hospital within less than 24 hours.

Additional studies that propose implementing new interventions during OHCA have used mannequins or simulations as a substitute for real patients.[40-42] This has the benefit of testing outcomes such as chest compression depth, ratio of adequate compressions, hands-off time, and clinician fatigue in the EMS setting, without endangering patients.[40] Unfortunately, the use of mannequins in OHCA trials precludes

the ability to measure vital outcomes such as survival and neurological status, and reduces generalizability. In order to study the effect that transthoracic echocardiography has on the survival of patients suffering OHCA, we have opted to enroll qualifying patients in our study, rather than use mannequins.

2.7.3 Inclusion and Exclusion Criteria

The exclusion criteria in our trial aim to exclude primarily patients who are of a vulnerable population, those who suffered traumatic arrests, or those who cannot or do not wish to be resuscitated. The exclusion criteria implemented by Nichol et al. were detailed by Brown et al. in a 2016 manuscript.[38,43] The populations selected for exclusion included:

> "patients with an EMS witnessed arrest; a written advance directive to not resuscitate; blunt, penetrating, or burn related injury; obvious cause of arrest is asphyxia, respiratory (asthma), drowning, strangulation, hanging, foreign body obstruction, or mechanical suffocation; uncontrolled bleeding or exsanguinations; known prisoners; known pregnancy; non-ROC EMS agency/provider first to initiate chest compressions or place pads; mechanical compression device used before any manual CPR by ROC personnel; advanced airway prior to ROC agency arrival; pre-existing tracheostomy; or a priori opted out from resuscitation research."[38,43]

These criteria closely match those proposed in our trial. Due to very low survival rates (ranging 0-3.1%), patients with cardiac arrest of a traumatic etiology are usually either excluded from OHCA trials, or studied separately.[44] Children, pregnant women, and prisoners are vulnerable populations that are also frequently excluded from such trials.

Hallstrom et al. used similar exclusion criteria as those used in the study by Nichol et al., with the addition of excluding patients who had had recent surgery.[39] Though the authors do not specifically address why patients with recent surgery were excluded, presumably this may be because patients with recent surgery may have characteristics that resemble those of patients who suffer traumatic cardiac arrests.

2.7.4 Baseline Characteristics of Patients

Many factors may affect survival in patients who suffer OHCA. Besides those demographic qualities that were discussed earlier in the review of confounding variables, many aspects of a cardiac arrest can affect whether an individual survives. Nichol et al. analyzed the following pretreatment characteristics in their study of the effect of continuous versus interrupted chest compressions on survival to hospital discharge: age, sex, obvious cause of arrest, arrest occurring in public location, witness status, bystander-initiated CPR, time from dispatch to first arrival of EMS, advanced life support on scene, and study site.[38] In the post-treatment characteristics, the authors included time between arrival of EMS and start of CPR, first rhythm (shockable vs. non-shockable), number of shocks given, prehospital intubation, CPR <6 min or until ROSC, drugs administered before arrival at hospital, and hospital procedures.[38] Many of these characteristics also encompassed sub-characteristics to further delineate what factors may have affected survival.[38] However, this study had a massive sample size (26,148), more than 10 times the sample size of the study proposed here.

Hallstrom et al. similarly designed a randomized controlled study implementing an intervention in the population of adult patients suffering OHCA and studying its effect on survival. The baseline characteristics analyzed in this study were similar but were not

separated by pre- and post-treatment characteristics.[39] The baseline characteristics

included here were age, sex, body type (thin, normal, obese, morbidly obese), witness of

arrest, CPR performed by bystander, public location of arrest, rhythm (shockable vs. non-

shockable), time from 9-1-1 call to unit arrival, time from 9-1-1 call to initial rhythm

assessment, time from 9-1-1 call to first shock, number of compressions, proportion of

first 5 minutes on ECG with compressions, advanced airway placed, IV line inserted,

epinephrine/vasopressin/bicarbonate administered, death on scene, transport to hospital,

and hypothermia therapy.[39]

Many of the baseline characteristics analyzed in our proposed study were drawn

from the two above studies. Although the authors of these studies proposed different

interventions than ours, they studied similar outcomes in a similar population with strong

randomized study designs with crossover. A prospective cohort study by Stiell et al.

examined the optimal chest compression depth by reviewing data from the ROC

PRIMED trial to correlate chest compression depth with survival.[45] The baseline

characteristics were more limited than those analyzed by the Nichol and Hallstrom

studies, but incorporated age, sex, bystander witness, bystander CPR, time to scene, time

to first shock, rhythm type, and other EMS interventions. Based on data from these

studies, we were able to compile a number of baseline characteristics to be analyzed in

the final data analysis portion of our proposed study.

2.7.5 Randomization Techniques

Data from the Nichol et al. trial and the Hallstrom et al. trial once again guided

the selection of randomization technique in our proposed study, due to the use of the

randomized crossover design in both trials. Nichol et al. enrolled 114 participating EMS

agencies, which were grouped into 47 clusters.[38] The clusters of agencies were subsequently randomly assigned to perform continuous chest compressions or interrupted chest compressions in a 1:1 ratio. Every six months, each cluster was crossed over to the other resuscitation strategy. Though our proposed study will enroll only four EMS agencies, these too will be clustered to include two in each cluster, which will then be randomized to intervention or control in a 1:1 ratio. Cluster randomization was also used by Hallstrom et al., with EMS agencies assigned to clusters within their site, and subsequently randomized to either control (manual CPR) or intervention (mechanical chest compression device) in a 1:1 ratio.[39] Crossover occurred at specified time intervals ranging from four weeks to two months. This randomization technique offers both convenience and effectiveness of intervention implementation in the setting of prehospital care. Hallstrom et al. specifically noted that the crossover design with cluster randomization allowed for convenience of device transfer.[39] In our proposed trial, this randomization technique combined with the study design allows for the purchase of fewer devices, and less time spent transferring devices between individuals. Perhaps even more importantly, cluster randomization at the institutional level diminishes the time spent making study-related decisions at the scene of a cardiac arrest, where time is crucial to the delivery of life-saving care.

2.7.6 Sample Size

As previously noted, there have been no randomized controlled studies examining the effect of prehospital echocardiography on survival in OHCA. However, there have been a few randomized controlled studies that have examined the effect of other prehospital interventions on the survival of patients suffering OHCA. These studies vary

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widely in terms of sample size. Nichol et al. enrolled a large sample size of 26,148

participants in their trial, which spanned 114 EMS agencies. Hallstrom et al. enrolled a

much smaller number of patients, totaling 1,071 participants. Both studies were able to

achieve statistical significance in either primary or secondary outcomes with their

respective approaches.

2.7.7 Informed Consent in Emergency Research

Obtaining consent for research in the prehospital setting can be quite challenging.

Prehospital emergencies often occur in austere environments and require time-sensitive

interventions. These challenges are further compounded when patients are unconscious,

as is the case with OHCA patients. To address challenges in obtaining informed consent

from patients in such dire circumstances, the Food and Drug Administration created a

protocol named the Exception From Informed Consent (EFIC) in 1996.[46] This policy

exists to protect the rights of vulnerable patients while still promoting progress in medical

research. According to the most recently updated guidelines, EFIC in emergency research

situations "may only be conducted in unexpected, life-threatening circumstances where

(1) the patient is incapacitated, (2) available treatments are unproven or unsatisfactory,

(3) the proposed intervention may benefit the patient directly, and (4) the therapy must be

initiated before consent from the [legally authorized representative] is feasible."[47] This

allows the trial to proceed without requiring researchers to immediately obtain consent;

instead, informed consent is obtained when the patient is no longer incapacitated, or a

legally authorized representative, such as a spouse or family member, is available to

provide informed consent for the patient. Furthermore, a "community consultation" is

implemented to ensure that members of the community can reflect on the details of the

study and raise potential concerns. In a 2014 study investigating the implementation of community consultations across a variety of communities, it was found that the most prevalent consultation method was attendance at meetings of existing community groups.[48] Knowledge of study content was high in these groups; increased study knowledge correlated with increased interactivity of the consultation.[48] The FDA furthermore requires that following the completion of the proposed trial, public disclosure is initiated to inform the community of the results of the study. Therefore, in order to protect the rights of patients, we will use the FDA-approved EFIC guidelines. The informed consent form can be found in Appendix 3.

2.8 Conclusion

Current evidence in emergency research suggests that, despite the advancement of resuscitation techniques, survival rates in OHCA remain low. Portable ultrasound devices have emerged as a novel tool that may be used in the prehospital setting to visualize pathology contributing to cardiac arrest and other morbidity. One potential application of these devices is in the setting of cardiac imaging; several studies have found that echocardiography during the peri-resuscitative period in prehospital cardiac arrest may lead to changes in treatment. There is evidence to suggest that it is feasible to teach paramedics, who make up the bulk of ALS clinicians in the prehospital setting in the United States, to perform echocardiographic assessments, correctly analyze the images, and apply this knowledge to patient care. Confounding variables may be plentiful in the setting of OHCA and survival outcomes, but the crossover study design will likely mitigate many of these effects. Evidence from previous studies supports the selection of the primary and secondary outcomes, as well as inclusion and exclusion criteria proposed

in this study. Cluster randomization has also been adopted from previous studies as a potentially convenient way to randomize subjects in a crossover study design, without delaying patient care. Finally, a great deal of care has been taken to determine the most ethical way to obtain informed consent in the prehospital setting; this trial will use a consent process consistent with the FDA-approved Exception From Informed Consent protocol.

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Chapter 3: Study Methods

3.1 Study Design

We will perform a prospective randomized crossover study involving four Connecticut-based ground ambulance services. The services in question are divisions of American Medical Response, Inc employing both BLS and ALS clinicians in Hartford, New Haven, Waterbury, and Bridgeport. The four divisions employ roughly 450 ALS clinicians who can participate in the trial, approximately equally distributed between the four sites. An initial two-month training period will be devoted to didactic and clinical education designed to train paramedics to perform focused echocardiographic assessments during CPR. The four divisions will then be randomized to initially either perform standard resuscitation on enrolled subjects or perform resuscitation with the aid of a portable ultrasound device to guide chest compression positioning, with two divisions in each group. The two divisions initially selected to be in the intervention group will receive an appropriate number of portable ultrasound devices to be distributed to all ALS units for use during cardiac arrest responses. Every two months the divisions will switch protocols, for a total of 20 months. Patients enrolled in the study will be followed for a total of 30 days after enrollment. An additional 30-day period will be devoted to data analysis. Figure 1 shows a depiction of the study design.
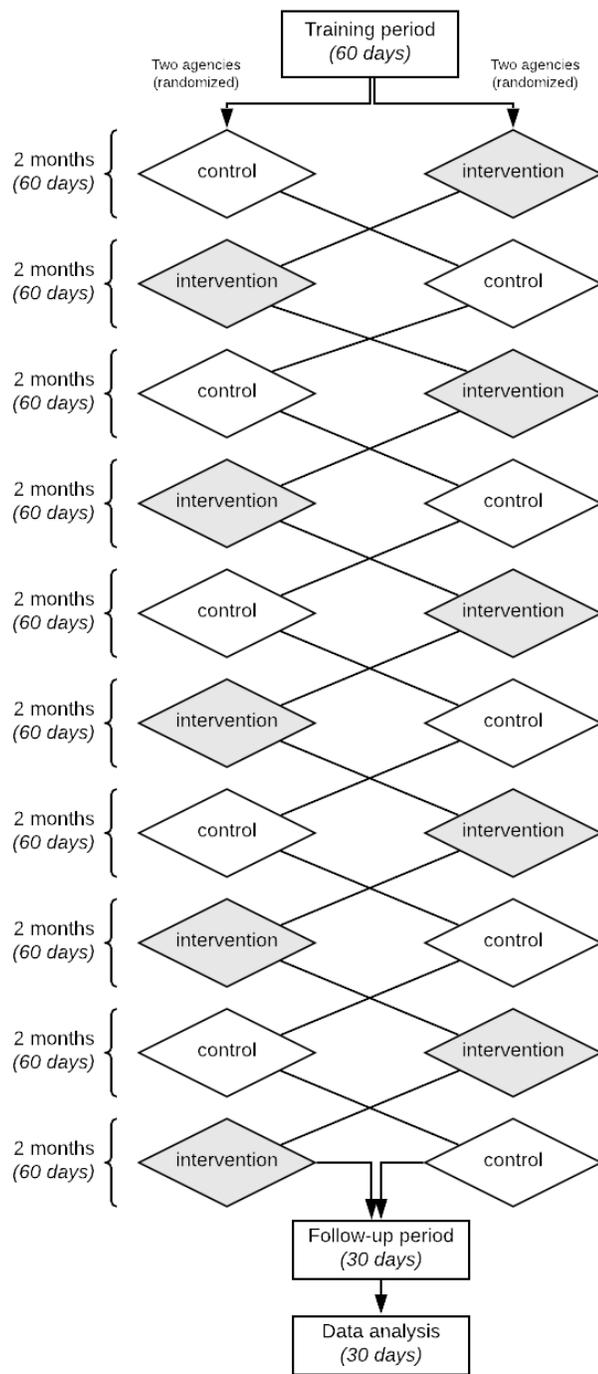
Figure 1: Study design protocol

3.2 Study Population and Sampling

The study population will include adults 18 and older suffering non-traumatic OHCA. Patients will automatically be excluded in cases where cardiopulmonary resuscitation is not indicated, such as those with appropriate 'do not resuscitate' (DNR) or advance directive orders in place, or obvious signs of death (lividity, decapitation, transection, rigor mortis). Patients will also be excluded if they are known to be part of a vulnerable population; these include children (ages <18), pregnant women, and prisoners or wards of state. Sampling of patients will occur in a consecutive sampling method; patients will be enrolled when an ALS unit arrives on scene and determines that the patient is in cardiac arrest, provided he or she does not meet the exclusion criteria to the best of the responding paramedic's knowledge.

3.3 Subject Protection and Confidentiality

Prior to the initiation of training, we will obtain institutional review board (IRB) approval by submitting an application according to the standard set in section 100 PR.1-Review by a Convened Institutional Review Board of Yale University. This application will include details of the process used to obtain informed consent as per guidelines of the Exception From Informed Consent emergency research protocol. The consent will explain the purpose of our research, procedures involved, and the duration of the study. It will also clearly delineate risks and discomforts of participation in the research protocol, as well as potential benefits. Though it will not be possible to obtain informed consent at the time of enrollment due to the nature of our research, informed consent will be obtained from the patient or a legally authorized representative as soon as possible. All data pertaining to patients will be deidentified wherever possible and stored in an

encrypted and password-protected server. Patients who do not wish to continue participating in the trial or have their data included in the study will have all data associated with their name removed from the server. Encryption of data, including protected health information, will be completed in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

As part of the EFIC guidelines for obtaining consent, we will also perform community consultations prior to the start of the trial but after IRB approval. The FDA requires community consultations to occur as a means of disseminating information about the study, including its risks and benefits. Prior to the start of the trial, we will take out several ads in local city newspapers (the Hartford Courant, the Waterbury Observer, the Connecticut Post, and the New Haven Register) detailing the goals, risks and benefits of participation in the trial, as well as details about where community consultations will occur and how enrollment will take place. After the study is complete, we will once again take out ads in these local newspapers reporting the findings of the study and thanking the community for its support and participation, as part of our public disclosure efforts.

As previously discussed, acceptance of EFIC protocol and recall of relevant study details was highest when community consultations were held in existing community groups and had interactive measures.[1] In order to provide the local community with an understanding of our proposed study and the enrollment process, we will plan a minimum of four community consultation gatherings during this time period. One community consultation will be performed in each of the communities that the four EMS agencies serve: Hartford, Waterbury, New Haven, and Bridgeport. Since the best results are produced when community consultations are held in existing community groups, the

scheduling of the consultations will depend on existing community gatherings at that time. The types of gatherings community consultations will occur in may include town hall forums, church groups, and club meetings. Community consultations will be advertised in advance. We will strive to ensure that attendance at the consultations is relatively equal across the four communities and will schedule additional consultations if necessary. During community consultations, we will explain pertinent study details, including risks and benefits of participation, as well as a description of the EFIC guidelines in layperson terms. At the conclusion of the meeting, surveys will be distributed to all participants to measure study detail recall and levels of agreement with EFIC enrollment. This process of community consultation will allow the members of the communities to develop basic knowledge of the trial and express any concerns that may need to be addressed prior to the start of the trial. Additionally, public disclosure of the findings of the study will provide the community with an understanding of the impact of the trial following its completion.

3.4 Recruitment

Whenever possible, an ALS unit staffed with an echocardiographic assessment-trained paramedic is sent to any cardiac arrest call that occurs within the jurisdictions of the four EMS services. In cases where an alternative dispatch turns out to be a patient in cardiac arrest, an eligible ALS unit responds as soon as possible. Local first responders (such as the police or fire departments) also respond. Patients will be enrolled in the trial when an ALS unit arrives on scene of the call and the paramedic determines that the patient is in cardiac arrest and does not meet any exclusion criteria. Since randomization will be occurring at the institutional level, there will be no delay in delivering life-saving

treatment to the patient. Unfortunately, in cases of OHCA, patient demographics and

causes of arrest are often unclear due to lack of bystander information and the patient's

inability to advocate for themselves. In cases where it is not clear whether the patient is in

cardiac arrest due to a traumatic cause, the patient will be enrolled, but then later

excluded in the final data analysis if he or she is found to have entered cardiac arrest

because of trauma. Similarly, in cases where the patient does not appear to be a child,

pregnant, or a prisoner, and there is no bystander information available to suggest

otherwise, the patient will be assumed to not be a part of these vulnerable populations.

3.5 Study Variables and Measures

The intervention will be paramedic-performed focused transthoracic

echocardiography using a portable ultrasound device performed during CPR. The control

patients will receive standard CPR according to statewide EMS protocols without

paramedic-performed focused transthoracic echocardiography.[2] The primary dependent

variable will be the proportion of patients surviving to hospital admission. Secondary

variables will include the proportion of patients in whom chest compression position is

adjusted, proportion of patients achieving ROSC, proportion of patients surviving to

hospital discharge, and neurological function at discharge (scored on modified Rankin

scale).

3.6 Blinding of Intervention

Patients will not be blinded to the intervention being performed, though most will

be unresponsive for the duration of their resuscitation due to the nature of cardiac arrest.

Therefore, the lack of subject blinding should not influence the results. The operators of

the interventions (EMS personnel) also cannot be blinded to the intervention. Hospital

personnel cannot be reliably blinded to the intervention either, since the results of the

echocardiography in the intervention group may lead to important changes in treatment of

the patient that may be vital in the EMS report given to triage personnel.

3.7 Blinding of Outcome

This will be a single-blinded study. The assessor of the outcome will be blinded to

whether each subject was in the control group or the intervention group. He or she will be

asked to assess the subject's medical record for survival data and neurological status,

without any knowledge of whether the subject received the intervention.

3.8 Assignment of Intervention

The initial randomization of the intervention among the four EMS services will be

performed by a computer program. Once randomized, the two pairs of services will swap

intervention/control every 60 days for the duration of the study; hence, randomization

will only occur once.

3.9 Adherence

Since the implementation of the intervention depends largely on the paramedics

providing primary treatment during a cardiac arrest, there will be several initiatives in

place to encourage their adherence to the protocol. A small monetary reward in the form

of a $20 Starbucks gift card will be awarded to all eligible paramedics who enroll patients

and use the intervention in at least 75% of eligible cardiac arrest patients they respond to.

Furthermore, in cases where eligible patients are not enrolled by paramedics, it will be

mandated that a "Non-Enrolled Patient" form be completed and reviewed to examine the

reasons for not implementing the intervention (see Appendix 1). Paramedics will be

required to sign the portable ultrasound devices out of the office with their charging

devices and return them at the end of their shift with details of any issues or damages that

may have occurred during the shift. Unfortunately, several prior studies have described

issues with paramedics adhering to study protocols in trials involving prehospital

interventions.[3,4] We believe that establishing several safeguards in place to encourage use

of the portable ultrasound devices will limit bias and confounding, and help enroll the

necessary number of participants to meet the required sample size.

3.10 Monitoring of Adverse Events

Similar studies have monitored a variety of adverse events in patients suffering

OHCA.[5,6] Using these studies as a frame of reference, we will review patient charts for

the following adverse events: death, re-arrest, pulmonary edema, seizure, chest fracture,

pneumothorax, hemothorax, cardiac tamponade, cerebral bleeding, aspiration, and

internal organ injury. These are adverse events that can occur as a result of the aggressive

resuscitation performed during CPR or ACLS. Paramedics will be asked to comment on

adverse events in the enrolled patient forms. Information about subsequent adverse events

will be obtained from the patient's medical record. The intervention itself (applying the

ultrasound probe to the chest) does not have any known serious adverse effects.

3.11 Data Collection

Data will be collected continually throughout the course of the trial. After the

initial two-month training period is complete, the 20-month enrollment period will begin.

Paramedics will be expected (and incentivized as above) to enroll eligible patients into

the trial when they are dispatched to cardiac arrests. Paramedics in the intervention group

will perform patient care as specified in the state protocols, with the only exception being

the use of the portable ultrasound device during chest compression intervals.[2] Paramedics who enroll a patient into the trial will be expected to fill out a "Cardiac Arrest Trial Enrollment Form" detailing whether they were able to elicit an adequate view using the portable ultrasound device, whether the left ventricle was being adequately perfused, and whether the imaging resulted in a change in compression positioning or patient management (Appendix 2). A short narrative will be written detailing any changes in patient management. Paramedics who do not enroll an eligible patient will complete a similar form explaining why they were unable to or did not wish to comply with the trial guidelines. Paramedics will be required to fill out the necessary forms the same day of their shift to maximize retention. We hope that these forms will shed light on the factors that contribute to changes in patient management, as well as possible equipment and compliance issues, without interfering with or delaying emergent patient care at the time of cardiac arrest.

Additional data on survival and adverse events will be collected from EMS run forms and hospital records. Data will be collected in the electronic medical records at Yale New Haven Hospital, Saint Francis Hospital, Hartford Hospital, Hospital of Central Connecticut, Saint Vincent's Hospital, Bridgeport Hospital, Waterbury Hospital, and Saint Mary's Hospital. A 30-day follow-up period ensures that we are able to collect the necessary data from patients who may be hospitalized for extended periods of time following cardiac arrest. Any patient who subsequently refuses to participate in the trial will have his or her records expunged from all data collected in this trial.

3.12 Sample Size Calculation

We are planning a study in which subjects will be randomized to either the intervention or control at the institutional level at an approximately equal ratio. The calculation of sample size is based on comparison of rates of survival to hospital admission in a population of patients suffering OHCA receiving standard care, and is averaged from several studies including those by Aichinger et al[7], Nichol et al[6], Hallstrom et al.[8], and Aufderheide et al[5]. The average rate of survival to hospital admission in the control groups of these studies is 24%. The study will be powered at 80%, with a type I error of 5%. Currently there are no randomized, controlled studies available on the use of ultrasound in prehospital cardiac arrest and its effect on survival.[9] We are aiming to observe a 5% increase in the proportion of patients surviving to hospital admission in the intervention group; this effect size was used in a similar study by Aufderheide et al.[5] Therefore, the calculated sample size is 1,222 patients in each group, for a total of 2,444 participants. See Appendix 6 for further sample size calculation details.

3.13 Statistical Analysis

Descriptive statistics will include age, sex, BMI, comorbidities, presumed cause of cardiac arrest, downtime (in minutes), location of arrest (whether public), bystander witness of arrest, bystander CPR, initial rhythm present, length of resuscitation (in minutes), time from 9-1-1 call to arrival of unit (in minutes), and time between arrival of EMS and CPR initiation (in minutes). Analysis will be performed under the intention-to-treat protocol. A significance level will be set as $p \leq 0.05$. Continuous variables will be represented as parametric means with standard deviation and will include the following:

age, BMI, downtime, length of resuscitation, time from 9-1-1 call to arrival of unit, and time between arrival of EMS and CPR initiation. If any of the baseline characteristics are found to be nonparametric, they will be represented as medians with interquartile ranges instead. Sex, occurrence of arrest in public area, bystander witness of arrest, and bystander CPR will be analyzed as proportions. Finally, comorbidities, presumed cause of arrest, and initial rhythm present will be analyzed as relative frequencies. The primary outcome, survival to hospital admission, will be analyzed as a proportion with McNemar's test due to the matching of crossover groups. Although the crossover study design minimizes the likelihood of imbalance of confounding variables between groups, multivariate analysis may need to be performed. In this case, a conditional logistic regression model will be used. Secondary variables analyzed using McNemar's test will include proportion of patients in whom chest compression position is adjusted, proportion of patients achieving ROSC, and proportion of patients surviving to hospital discharge. Neurological function at discharge (scored on modified Rankin scale) will be analyzed as a median using the Wilcoxon signed-rank test. With the exception of neurological function, which will be analyzed using the ordinal logistic regression model, multivariate analysis of all other secondary outcomes will be performed using the conditional logistic regression model.

Characteristic	Study Participants
Age (years)	
Sex (% male, % female)	
BMI (kg/m2)	
Comorbidities (HTN, DM, COPD, atrial fibrillation, heart disease, CHF, cancer, pacemaker, other)	
Presumed cause of arrest (% cardiac, medical non-cardiac, intoxication, choking, other/unknown)	
Downtime (minutes)	
Occurrence in public area (%)	
Bystander witness of arrest (%)	
Bystander CPR (%)	
Initial rhythm present (% shockable, non-shockable, unknown/unavailable)	
Length of resuscitation (minutes)	
Time from 9-1-1 call to arrival of unit (minutes)	
Time between arrival of EMS and CPR initiation (minutes)	

Table 1: Descriptive characteristics of enrolled patients

3.14 Timeline and Resources

The study period will be 24 months, beginning in January 2021. Prior to this time, we will request approval from the Human Investigation Committee, which will take approximately 3 months. From January 1, 2021 – March 1, 2021, paramedics in the four AMR agencies will be assigned to didactic echocardiography training. Previous studies have shown that paramedics can successfully obtain good images of the heart following a single day of training that incorporates both didactic and practical sessions.[4,10] A two-

hour didactic lecture will be followed by a two-hour long period of practice on an ultrasound simulator and practice on volunteers. The didactic session will focus on using the parasternal long axis (PSLA) and subxiphoid views for identification of the following components of echocardiography: movement (presence of), function (quality of), and chambers (particularly the left ventricle).[10] The simulation and practice session will be necessary to ensure that paramedics become comfortable with the equipment and learn how to use it to obtain the correct views. The goal of the training will be to obtain a satisfactory view of the left ventricle from the two views while compressions are being simulated in <30 seconds. Paramedics will complete a short quiz at the end of the four-hour classroom training to test their knowledge and new skills. Paramedics will be shown ultrasound clips and asked to identify the left ventricle and its quality of function. Paramedics will also briefly be tested on their ability to obtain PSLA and subxiphoid views on a volunteer in under 30 seconds. Paramedics who score <70% on the administered quiz will be required to attend refresher training prior to participating in the trial.

Following the four hours of classroom training and quiz, each paramedic will also complete a scheduled 12-hour training shift in his or her sponsor hospital's emergency department, to practice performing the echocardiographic assessment on living patients. If a patient in cardiac arrest presents to the emergency department, the paramedic will have the opportunity to perform the echocardiographic assessment on the patient in cardiac arrest. Paramedics who are newly hired after the trial has started, or those who require additional training, will have the opportunity to attend a four-hour "refresher" training session held monthly at one of the central stations of the EMS agencies.

From March 1, 2021 – November 1, 2021, patients will be enrolled into the study by trained paramedics. This 20-month period ensures that there is ample time to enroll enough patients to reach the desired sample size. A 30-day follow-up period will begin once the enrollment period is over. We estimate that an additional 30-day period will be required for data analysis. The equipment requirement for this study will be approximately 60 portable ultrasound devices. This is estimated based on the approximation of 30 ALS units available for coverage on a given day at each EMS agency. Since only half of the agencies will have portable ultrasound devices at any given time, we can purchase enough portable ultrasound devices to be used at two agencies 24 hours a day. We will use Butterfly IQ probes, which are relatively small and durable, and thus likely to survive the harsher conditions in the field relative to hospitals. At approximately $2000 a unit, we estimate that the total cost of the devices will be approximately $120,000. Paramedics will use their own smartphones to connect to the device and view images, whenever possible. We will approach the manufacturer regarding providing portable ultrasound devices at a discounted rate due to the volume of the order. The study will also require a minimum of one training instructor to deliver didactic and hands-on training. We will also need to employ a project oversight manager to collect data from the EMS agencies and ensure it is properly entered into the project database according to HIPAA standards.

Chapter References

1. Dickert NW, Mah VA, Biros MH, et al. Consulting communities when patients cannot consent: a multicenter study of community consultation for research in emergency settings. *Crit Care Med.* 2014;42(2):272-280.
2. Services OoEM. Connecticut Statewide Emergency Medical Services Protocols v. 2019.4. In: Health CDoP, ed. Hartford, CT: CT Department of Public Health; 2019.
3. Ketelaars R, Beekers C, Van Geffen GJ, Scheffer GJ, Hoogerwerf N. Prehospital Echocardiography During Resuscitation Impacts Treatment in a Physician-Staffed Helicopter Emergency Medical Service: an Observational Study. *Prehospital Emergency Care.* 2018;22(4):406-413.
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5. Aufderheide TP, Frascone RJ, Wayne MA, et al. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: a randomised trial. *Lancet.* 2011;377(9762):301-311.
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Chapter 4: Conclusion

4.1 Advantages and Disadvantages

The trial we have proposed here has several advantages. The intervention we are implementing makes use of technology that is both effective and relatively inexpensive. The study we have proposed investigates the effect of portable ultrasound technology in the prehospital setting on survival to hospital admission, which has not been studied in this context. As such, the results gathered from this study may provide the first data available on the effect of this type of technology on survival in the prehospital setting. The primary and secondary outcomes will provide data on survival to both hospital admission and discharge, as well as neurological function at discharge. These data may provide some insight not only on the survivability of cardiac arrest, but long-term patient health as well. The study design is a randomized prospective crossover trial, which has several benefits. The crossover design allows for greater convenience and decreases costs, because it allows researchers to purchase fewer pieces of equipment. Because each participant is matched due to the inherent structure of the crossover design, confounding is mitigated. Another benefit of the study we have proposed is that it incorporates paramedics from American Medical Response, Inc, a corporation that already has several structured EMS agencies across Connecticut, and a national commitment to advancing EMS research. The four EMS agencies we will be using to enroll patients cover diverse and widespread areas of Connecticut, encompassing urban, suburban, and rural communities. This ensures that we will be able to enroll participants from different backgrounds with a wide variety of baseline characteristics. This in turn will allow for

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greater generalizability of results. Furthermore, because the four agencies collectively employ approximately 450 paramedics and staff approximately 120 on any given day, we will easily be able to enroll an adequate number of participants in our study to meet the required sample size and appropriately power the study. We have determined that it is feasible to train paramedics to perform and analyze the assessment we have proposed, as described in Chapter 2. The paramedics who participate in our study will undergo a training period that is extensive enough to ensure that they have all the necessary skills to perform the echocardiographic assessment, based on data from prior studies.[1-3] The study timeline, which incorporates a 20-month participant enrollment period, allows ample time to meet the sample size. The 30-day follow-up period additionally ensures that patients who survive to hospital admission and remain admitted can be followed for an additional month to track secondary outcomes.

Although our proposed study has many advantages, there are also several disadvantages associated with the nature of prehospital medicine. Unfortunately, it is impossible to obtain traditional informed consent in a prehospital setting where patients are unconscious. We will utilize the EFIC protocol to obtain informed consent from the participant or a legally authorized representative as soon as possible, but this process is not ideal.[4] However, this currently remains the only viable way to perform research in emergency medicine when participants are incapacitated. Another challenge to our study's validity that may arise is the possible lack of adherence to study protocols by participating paramedics, which is an issue that has arisen in other studies using paramedics in the prehospital setting.[5] Ketelaars et al. found that due to many different possible factors (including lack of time, forgetfulness, and perceived lack of "usefulness"

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of the images obtained), paramedics often omitted data or case report forms from the trial, resulting in unwanted selection bias. These issues may certainly arise in our proposed study, but we have taken several steps to preemptively prevent this. Paramedics will be offered a small monetary incentive for enrolling patients and filling out the associated form (see Appendix 2). Furthermore, paramedics will also be required to submit paperwork when they fail to enroll patients (see Appendix 1) to determine where and why the failure occurred.

4.2 Clinical and/or Public Health Significance

As previously described, there currently are no randomized controlled studies available examining the effect of prehospital ultrasound use on survival. Our proposed study will result in the first set of data that examines how the use of ultrasound in the prehospital setting affects survival rates. Because portable ultrasound devices may seem to be a large monetary investment to many small EMS agencies, ultrasound technology is still not widely available in the prehospital setting. If found to be positive, the evidence garnered in this study could help support the decision to purchase ultrasound devices or apply for grants or funding from local organizations to do so. Additionally, the data from this study could have implications for how CPR is currently standardized. Since body habitus and anatomical variations are currently not accounted for when performing CPR, the data from this trial may show whether this needs to change to involve an individualized approach to resuscitation. CPR is one of the most important components of early care of cardiac arrest, yet it relies on the assumption that every person's body will be identically receptive to compressions. With the findings from this trial, we may be

able to provide evidence to support a new method of CPR delivery that accounts for

individual anatomy.

<u>Chapter References</u>

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3. Reed MJ, Gibson L, Dewar A, Short S, Black P, Clegg GR. Introduction of paramedic led Echo in Life Support into the pre-hospital environment: The PUCA study. *Resuscitation.* 2017;112:65-69.
4. Services USDoHaH. Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research In: Administration FaD, ed. Silver Spring, MD2013.
5. Ketelaars R, Beekers C, Van Geffen GJ, Scheffer GJ, Hoogerwerf N. Prehospital Echocardiography During Resuscitation Impacts Treatment in a Physician-Staffed Helicopter Emergency Medical Service: an Observational Study. *Prehospital Emergency Care.* 2018;22(4):406-413.

Appendices

Appendix 1: Non-Enrolled Patient Form

Non-Enrolled Patient Form for Cardiac Arrest

Your Name: _____

Employee Number: _____

Date: _____

Patient Initials: _____

Patient DOB: _____

Presumed Cause of Arrest (if known): _____

Please check off the following reasons for why the portable ultrasound device was not used during the cardiac arrest (*select all*):

□ Patient was not eligible for the study. *Please explain why:* _____

□ Probe was not available

□ Probe was not charged

□ Other technical difficulty using probe

□ Forgot to use

□ Did not know how to use

□ Other: _____

Elaborate on the above - Please explain why the portable ultrasound device was not used to evaluate the efficacy of CPR during this cardiac arrest:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Appendix 2: Enrolled Patient Form

Cardiac Arrest Trial Enrollment Form

Your Name: _____

Employee Number: _____

Date: _____

Patient Initials: _____

Patient DOB: _____

Presumed Cause of Arrest (if known): _____

1. Were you able to get an adequate view of the heart during chest compressions using the ultrasound probe?

□ Yes

□ No

2. If you answered "yes" above, was the left ventricle being adequately compressed during CPR?

□ Yes

□ No

□ Not sure

3. Did the view on ultrasound lead to a change in chest compression positioning OR a change in patient management?

□ Yes

□ No

4. If you answered "yes" above, please elaborate on what changes in patient management occurred based on the ultrasound view:

_____
_____
_____
_____
_____
_____
_____
_____
_____

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A
RESEARCH STUDY

YALE UNIVERSITY SCHOOL OF MEDICINE

YALE-NEW HAVEN HOSPITAL

Study Title: Effect of prehospital echocardiography in cardiac arrest to augment
positioning of chest compressions

Principal Investigator (the person who is responsible for this research): Alexandra
Zhakov

Phone Number: (860) 816-6356

Research Study Summary:

- We are asking you to continue being a part of our research study.
- The purpose of this research study is to determine whether the use of paramedic-guided echocardiography during cardiopulmonary resuscitation in out-of-hospital cardiac arrest results in higher rates of survival to hospital admission.
- Study procedures will include: There are two groups in this project. You were enrolled in one of the two groups based on which branch of emergency medical services responded to your 9-1-1 call for help. One group received the intervention, which is the use of echocardiography during cardiopulmonary resuscitation. The other group is the control, which means that people in this group receive standard cardiopulmonary resuscitation as dictated by Connecticut emergency medical services protocols.
- There are no risks to continuing your participation in this study.
- Taking part in the continuation of this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to continue to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because **you suffered an out-of-hospital cardiac arrest and were given life-supporting care by emergency medical services personnel**.

Who is paying for the study?

Yale School of Medicine Physician Associate Program

What is the study about?

The purpose of this study is to determine whether the use of transthoracic echocardiography during cardiopulmonary resuscitation will lead to higher rates of survival to hospital admission. Transthoracic echocardiography is performed using a Butterfly IQ portable ultrasound device, which was FDA-approved in 2017 for many clinical purposes, including cardiac imaging. We use the Butterfly IQ ultrasound probe to image the heart while it is being compressed during cardiopulmonary resuscitation.

What are you asking me to do and how long will it take?

You are being asked to continue to participate in this study because you suffered a medical cardiac arrest outside of a hospital, and a bystander or loved one called 9-1-1 to activate emergency medical services for help. The dispatcher sent an ambulance with personnel who had advanced life support credentials. These personnel, the paramedics, were instructed on how to follow this study's protocols without delay of emergency care. The paramedic assessed you, and instructed others to begin life-saving care. At the same time, he or she determined that you met other criteria (such as being an adult, not pregnant, not having any "do not resuscitate" directives, and not having been involved in a traumatic event causing the cardiac arrest). You met enrollment criteria, and the paramedic determined that you could participate in the trial. However, he or she did not randomize you to the intervention or control group at that time. Randomization had already occurred at the institutional level, meaning the paramedic was told in advance whether the patients he or she enrolls will be in the intervention group or control group. Unfortunately, the paramedic was not able to obtain informed consent from you or a legally authorized representative at that time, because you were unresponsive and delaying care would have been unethical. **In cases like these, researchers are able to enroll you in an emergency research trial provided that you or a legally authorized representative give informed consent to continue participating in the trial as soon as possible.**

If you were in the control group, you received standard care, including cardiopulmonary

resuscitation, as per statewide emergency medical services protocols. This means that the paramedic and the rest of the emergency team did everything in their power to resuscitate you. If you were in the intervention group, the paramedic and the rest of the team delivered the same exact care as directed by statewide protocols, with one small exception. While a member of the team was performing chest compressions to re-perfuse your heart, the paramedic used a small, portable ultrasound probe to visualize your heart by placing it over your chest. The probe uses soundwave technology to show an image of the heart to the paramedic in real time. The images received by the probe allowed the paramedic to determine whether the heart was pumping effectively during CPR, or whether a small adjustment in positioning of chest compressions needed to be made. If so, the paramedic would have asked the teammate performing chest compressions to adjust his or her form, without interrupting CPR. This should not have affected your care in any detrimental way, because CPR was not paused. The rest of your care was also not changed.

You were transported to the hospital, and there you were registered and your care continued as usual. Since the study aims to determine whether there will be an increase in survival to hospital admission, an outcome assessor will need to view your medical record, but he or she will not know whether you were in the intervention or control group. Your consent is needed to use the information we have already collected, and to have the outcome assessor view your record.

What are the risks and discomforts of participating?

There are minimal side effects associated with transthoracic echocardiography. This intervention is not invasive. It involves placing a probe on the skin over your heart and taking an image. This already took place; no further interventions are involved.

Direct side effects:

The main side effects that other people have experienced so far with transthoracic echocardiography is discomfort from the ultrasound probe. However, this already took place.

Additional side effects:

Another risk may be the paramedics' inexperience with a new tool. Paramedics have been trained to use the ultrasound probe with the explicit request that no other aspects of patient care change. However, there are other paramedics present on the team that responded to your emergency, who have not been previously exposed to this device. We cannot guarantee that there were no changes to the speed with which care is delivered by these personnel, as they adjust to the implementation of a new device in the resuscitation

algorithm. Every effort has been made to train the paramedics involved in this protocol to limit the amount of time spent performing the intervention in order to limit distractions and delays in care. If you have questions, you can talk to the project director about whether this risk may have applied to you.

Reproductive risks:

We do not know if the intervention causes harm to a baby, so we do not want anyone who might be pregnant to enter the project.

How will I know about new risks or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study.

How can the study possibly benefit me?

This study may or may not help you, but we hope the information from this study will help us develop better treatments for cardiac arrest. This intervention is unlikely to worsen your condition. Cardiac arrest, especially when occurring outside of a hospital, has a very low survival rate. Your chances of survival depend largely on how well your heart is perfused after you suffer a cardiac arrest. This intervention will attempt to lessen the amount of time that your heart, brain, and other vital organs are poorly perfused. If successful, this intervention may increase the likelihood of survival from cardiac arrest.

How can the study possibly benefit other people?

The benefits to science and other people may include a better understanding of how CPR can be tailored to each individual person's anatomy.

Are there any costs to participation?

You will not have to pay for taking part in this study.

Will I be paid for participation?

You will not be paid for taking part in this study.

How will you keep my data safe and private?

We will keep information we collect about you confidential. We will share it with others if you agree to it or when we have to do it because U.S. or state law requires it. We will keep all data related to your care password protected in a secure database.

When we publish the results of the research or talk about it in conferences, we will not use your name or other identifying information, such as your address or date of birth. We will also not share information about you with other researchers for future research.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by **the fire department that responded to your cardiac arrest (if any), American Medical Response, Inc. (if they transported you to the hospital), and associated hospitals** created from: **1/1/2021** to: **1/1/2023**
- Records about phone calls made as part of this research
- Records about your study visit
- Information obtained during this research regarding
    - Records about your medical condition
    - Records about the study device

How will you use and share my information?

We will use your information to conduct the study described in this consent form.

We may share your information with:
- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring

research compliance. These individuals are required to keep all information confidential.

- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about **the portable ultrasound device** involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The study sponsor or manufacturer of study drug/device
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to continue to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to **Alexandra Zhakov** at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctors outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to insure the integrity of the study and/or study oversight.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever

choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. **This may occur if you are discovered to not meet enrollment criteria, such as if you are: pregnant, under 18 years of age, a prisoner, or ward of state.**

What will happen with my data if I stop participating?

If you decide to stop participating in the study, all data and images associated with your name will be deleted from our database.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at **(860) 816-6356).**

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

_____   _____   _____
Participant Printed Name   Participant Signature   Date

_____   _____   _____
Person Obtaining Consent   Person Obtaining Consent   Date
Printed Name   Signature

_____   _____   _____
Legally Authorized Representative   LAR Signature   Date
Name

_____   _____   _____

Complete if the participant is not fluent in English and an interpreter was used to
obtain consent. Participants who do not read or understand English must not sign this
full consent form, but instead sign the short form translated into their native
language. This form should be signed by the investigator and interpreter only. If the
interpreter is affiliated with the study team, the signature of an impartial witness is also
required.

Print name of interpreter: _____

Signature of interpreter: _____   Date: _____

An oral translation of this document was administered to the participant in

_____ (state language) by an individual proficient in English and

_____ (state language).

Print name of impartial witness: _____

Signature of impartial witness: _____
Date: _____

Appendix 4: Instrument Used to Visualize Cardiac Contractility

<u>Image 1:</u> The Butterfly IQ probe attaches to smartphones and will be used by the paramedic to visualize the left ventricle during cardiac arrest. It contains a built-in battery which can be wirelessly charged. The device can perform up to 2 hours of continuous scanning on a full charge.[1]

Reference:
1. Canepa CA, Harris NS. Ultrasound in Austere Environments. *High Alt. Med. Biol.* 2019;20(2):103-111.

Appendix 5: Modified PSLA and Subxiphoid Views Obtained During CPR

The following images (provided by Liu et al.) depict how a clinician obtains the PSLA and subxiphoid views while chest compressions are in progress.[2]

Image 1: A clinician obtains a modified PSLA view while another administers manual chest compressions.

Image 2: A clinician obtains a subxiphoid view while automated chest compressions are in progress.

Reference:
1. Liu RB, Bogucki S, Marcolini EG, et al. Guiding Cardiopulmonary Resuscitation with Focused Echocardiography: A Report of Five Cases. *Prehosp Emerg Care.* 2019:1-9.

Appendix 6: Sample Size Calculation

Sample size based on a proportion calculator with assumed normal distribution.

- Alpha (a) = 0.05 (two-tailed)
- Beta (b) = 0.20, corresponding to 80% power
- Risk in control group = $P_0 = 0.24$
- Risk in intervention group = $P_1 = 0.29$
- Effect size = 5%

Sample size – Proportions

Compare proportion with a dichotomous outcome between two samples, using the Chi-squared statistic (or z test).

Instructions: Enter parameters in the red cells. Answer will appear in the blue cells.

α (two-tailed) =	0.050	Threshold probability for rejecting the null hypothesis. Type I error rate.
β =	0.200	Probability of failing to reject the null hypothesis under the alternative hypothesis. Type II error rate.
q_1 =	0.500	Proportion of subjects that are in Group 1 (exposed)
q_0 =	0.500	Proportion of subjects that are in Group 0 (unexposed); $1-q_1$
P_0 =	0.2400	Risk in Group 0 (baseline risk)

Enter any ONE of the following three parameters (the other two will be calculated automatically):

P_1 =	0.2900	Risk in Group 1 (exposed)
OR =	1.293	Odds ratio $(P_1/(1 - P_1))/(P_0/(1-P_0))$
RR =	1.208	Risk ratio (P_1 to P_0)

[Calculate]

The standard normal deviate for $\alpha = Z_\alpha = 1.960$
The standard normal deviate for $\beta = Z_\beta = 0.842$
Pooled proportion = $P = (q_1 {*} P_1) + (q_0 {*} P_0) = 0.265$
$A = Z_\alpha \sqrt{P(1-P)(1/q_1 + 1/q_0)} = 1.730$
$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)} = 0.742$
$C = (P_1-P_0)^2 = 0.003$
Total group size = $N = (A+B)^2/C = 2{,}444$
Continuity correction (added to N for Group 0) = $CC = 1/(q_1 * |P_1-P_0|) = 40$

Sample size (without continuity correction)			
	N	**Outcome+**	**Outcome-**
Group 1:	1222	354	868
Group 0:	1222	293	929
Total:	2444	647	1797

Calculators used: Power and Precision 4.0, cross-referenced with UCSF Sample Size Calculator (https://www.sample-size.net/sample-size-proportions/)

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