Smartphone ECG for evaluation of ST-segment elevation myocardial infarction (STEMI): Design of the ST LEUIS International Multicenter Study

Alejandro Barbagelata, MD,a Charles F. Bethea, MD, b Harry W. Severance, MD, c Robert J. Mentz, MD,d David Albert, MD,e Gregory W. Barsness, MD,f Viet T. Le, PA-C, g Jeffrey L. Anderson, MD,g,h T. Jared Bunch, MD, g,i Frank Yanowitz, MD,g,h Benjamin Chisum, BS,g Brianna S. Ronnow, MS,g Joseph B. Muhlestein, MDg,h,*

a Catholic University, Buenos Aires, Argentina
b Integris Heart Hospital, Oklahoma City, OK, United States
c Erlanger Institute for Clinical Research, UT College of Medicine, Chattanooga, TN, United States
d Duke University, Durham, NC, United States
e AliveCor™ Corporation, San Francisco, CA, United States
f Mayo Clinic, Rochester, MN, United States
g Intermountain Medical Center, Intermountain Heart Institute, Salt Lake City, UT, United States
h The University of Utah, Department of Internal Medicine, Salt Lake City, UT, United States
i Stanford University, Department of Internal Medicine, Palo Alto, CA, United States

Abstract

In patients experiencing an ST-elevation myocardial infarction (STEMI), rapid diagnosis and immediate access to reperfusion therapy leads to optimal clinical outcomes. The rate-limiting step in STEMI diagnosis is the availability and performance of a 12–lead ECG. Recent technology has provided access to a reliable means of obtaining an ECG reading through a smartphone application (app) that works with an attachment providing all 12–leads of a standard ECG system. The ST LEUIS study was designed to validate the smartphone ECG app and its ability to accurately assess the presence or absence of STEMI in patients presenting with chest pain compared with the gold standard 12–lead ECG. We aimed to support the diagnostic utility of smartphone technology to provide a timely diagnosis and treatment of STEMI. The study will take place over 12 months at five institutions. Approximately 60 patients will be enrolled per institution, for a total recruitment of 300 patients. © 2017 Elsevier Inc. All rights reserved.

Keywords:
ECG; STEMI; Smartphone; Myocardial infarction

Introduction

In acute coronary syndrome (ACS), the pathology of ST-elevation myocardial infarction (STEMI) is associated with acute total occlusion of the coronary artery lumen, whether from thrombus or other mediating factors. To obtain the best clinical outcome, STEMI patients require immediate catheter-based or pharmacologic reperfusion therapy [1,2]. It has been reported that one third of patients with non-reperfused STEMI will die within the first 24 h of the event [3]. The majority of STEMI deaths occur in the prehospital setting within the first 1 to 2 h and usually from an associated cardiac arrhythmia known as ventricular fibrillation [1]. It appears many patients experiencing a STEMI do not typically seek medical care for up to 2 h after symptom onset [4–6]. Barriers to early reperfusion have been described and include such issues as lack of identification of STEMI, misattributing symptoms of STEMI to some other disease, fearing embarrassment of false alarm, not fitting a “stereotype” for heart disease, and lack of recognition by bystanders of a STEMI event [1,7].

The recently launched AHA Mission Lifeline initiative aims to increase the number of patients with timely access to reperfusion by addressing the continuum of care for STEMI, beginning with patient recognition of symptoms. EMS activation is critical not only for rapid transport to a center...
capable of providing the proper intervention, but also for early assessment and triage, including a prehospital 12-lead ECG.

ECG is frequently used in the field by on-scene emergency medical personnel to assess for fatal electrical rhythms and/or ACS prior to transport to area hospitals for treatment. If ST elevation is present, because of the probable need for immediate reperfusion therapy, an emergent status is usually declared and rapid transport to a hospital capable of performing primary PCI is provided. Of course, further in-hospital testing, with serum cardiac markers and serial ECGs, will be required to confirm the presence or absence of myocardial infarction. But the initial 12-lead ECG is critical to appropriately guide the patient’s initial management. Given that earlier treatment of STEMI reduces mortality and morbidity [2,3,8,9], it is thus important to increase the speed with which one recognizes that a STEMI event is occurring.

Despite the 2013 ACCF/AHA STEMI guidelines recommendation that EMS obtain an ECG within 10 min of first medical contact, it has been shown that only 27% of patients transported by EMS receive an ECG prior to arriving at the hospital [10]. Despite availability of equipment [11] and a class I indication [2], in many cases the equipment appears to be underutilized. For these as well as other system issues, there currently are a large number of patients suffering significant system delays in diagnosis and too frequent transfer to a non-PCI facility leading to an increase in mortality and heart failure [12].

Given that earlier treatment of STEMI reduces mortality and morbidity [3,8,9], it becomes important to increase the speed with which one recognizes that a STEMI event is occurring. As ECG is the method for diagnosing STEMI and is also the most simple and accessible diagnostic modality, it is proposed that earlier detection of STEMI and thus potentially more timely intervention may be accomplished by increasing access to a reliable means of obtaining an ECG reading, i.e., as through an electronic device that has become widespread.

Smartphone technologies have become widespread and readily available in both wealthy and poor nations, i.e., have become nearly ubiquitous in their presence and penetrance across the world. A 2016 report from the Pew Research Center estimates that nearly three quarters of the US population own a smartphone [13].

Several medical applications (apps) have been developed in recent years with the idea of improving point of care contacts and increasing patient access to timely care, including ECG apps for assessing real-time dysrhythmias. One such app works in tandem with simple peripheral hardware with sensors embedded and provides a single channel lead for accurate rate and rhythm assessment [14,15]. A newer prototype has been developed as a smartphone ECG system that has the potential to provide all 12-lead recordings of a standard 12-lead ECG system. This device, once proven to provide reliable and accurate diagnosis, may be able to be used also by non-medical personnel throughout the world. In wealthy nations, people could take the app and device on their phones when they travel into the wilderness or other remote locations. Then, if a member of their group experiences chest pain, they could transmit the ECG to be reviewed immediately at a distant hospital or by a qualified and designated healthcare provider. This could provide vital information for rescuers regarding the urgency of the situation. In poor countries, where standard ECG machines are not generally available, this device could provide inexpensive access to a reliable 12-lead ECG tracing by even trained medical personnel. Such a device might also be found attractive to volunteer or less well financed EMS services not able to afford current 12-lead transmission equipment, but that still have the potential for transporting patients to an appropriate STEMI reperfusion center.

A pilot study evaluating this new technology was recently published [16]. In this pilot trial, six patients presenting with ischemic myocardial symptoms for which a STEMI protocol was activated were enrolled. Simultaneous standard 12-lead ECGs and 12-lead smartphone ECGs were obtained and evaluated by a trial-selected panel of acknowledged ECG expert reviewers. The consensus of the review panel was that, in each case, the 12-lead smartphone ECG was similar enough to the standard 12-lead ECG in this ‘proof-of-technology’ study to justify a larger trial to further validate the smartphone ECG as an effective, less costly, and potentially more readily available alternative for the electrocardiographic diagnosis of STEMI.

We therefore proposed to validate the mobile smartphone ECG app and the device’s ability to accurately assess the presence or absence of a STEMI event in a larger cross-section of patients presenting with chest pain against the gold standard 12-lead ECG across multiple healthcare systems. By doing so, we aimed to increase the applicability of the device in a community setting to provide a timely diagnosis and treatment of these life-threatening events.

Study design

The ST LEUIS Study is a multicenter, international, prospective, non-randomized, open study, with a single-patient clinical trial design (i.e., the patients serve as their own control) comparing the smartphone ECG with a standard 12-lead ECG for diagnosing STEMI. It will take place over a 12 month period at 5 different institutions. The study will enroll approximately 60 patients at each institution, for a total recruitment of 300 patients. All patient participation in the study will take place on one day with no follow up visits required. ECG reading will be performed independently by a panel of experts, blinded to clinical diagnosis.

Study objectives and endpoints

The primary objective of this study is to determine whether the 12-lead smartphone ECG is an acceptable replacement for a standard 12-lead ECG in the identification of STEMI. Toward this primary objective, this study aims to:

1) Obtain simultaneous recordings of a standard 12-lead ECG and the smartphone “12-lead equivalent” ECG on patients presenting with chest pain for which the STEMI protocol was activated,
2) Obtain simultaneous recordings of a standard 12-lead ECG and the smartphone “12-lead equivalent” ECG on patients presenting to the Emergency Department for evaluation of chest pain, not necessarily presenting with STEMI.

3) Assess the operational feasibility of using the smartphone to obtain “12-lead equivalent” ECG recordings in patients suspected to have STEMI, or those presenting with chest pain in which STEMI is a possibility, and

4) Determine sensitivity, specificity, the positive predictive value and negative predictive value of the 12-lead smartphone ECG, using a paired standard 12-lead ECG as the gold standard.

**Study population**

Patients who are seen for chest pain at the Emergency Departments of the participating institutions, and/or patients for whom the STEMI protocol has been activated will be screened for this study. The patient’s history and medical records will be reviewed in order to evaluate the patient in relation to the inclusion and exclusion criteria (Table 1). Patients who meet eligibility criteria will be enrolled in the study upon completion of written informed consent. This will be done at the emergency department or the cardiac catheterization laboratory, as appropriate.

Within this study, two different populations will be studied. First, patients for which a STEMI protocol has been initiated, and secondly, patients presenting at the emergency department with chest pain. Using the lowest reported sensitivity of 87% and specificity of 90% from prior studies evaluating the smartphone ECG, and using a precision of 93% and a STEMI prevalence of one-third of the total study population, we estimate that 270 patients will be needed to evaluate the smartphone ECG. Therefore, a total of 300 patients will be enrolled to account for a 10% drop-out or lost to follow-up rate.

All sites participating in this study will obtain approval from their individual institutional review board (IRB) prior to enrolling patients. All sites will follow the requirements of their IRB. Informed consent will be obtained for all patients prior to enrollment in the study. The ST LEUIS study has begun enrollment in all five institutions, including four in the USA and one in Argentina.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Male or female ≥ 18 years of age.</td>
</tr>
<tr>
<td>2. Ability to understand and sign a written informed consent form, which must be obtained prior to initiation of any study procedures.</td>
</tr>
<tr>
<td>3. Symptoms of chest pain upon presentation at the Emergency Department of the participating institution.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inability or refusal of the patient and/or the patient’s legally-acceptable representative to provide written informed consent for any reason.</td>
</tr>
<tr>
<td>2. Other conditions that in the opinion of the Lead Investigator may increase risk to the subject and/or compromise the quality of the clinical trial.</td>
</tr>
</tbody>
</table>

**Study procedures**

Once enrolled in the study, patients will be classified into one of two groups, 1) those presenting to the hospital for which the STEMI protocol is activated, and 2) those presenting with chest pain in which the hospital STEMI protocol is not activated. A standard 12-lead ECG will be completed, immediately followed by the smartphone ECG using the AliveCor™ Heart Monitor and application software. For this study, the AliveCor™ Heart Monitor and application software will be used with an identical 5th generation iPod Touch provided to each institution (Fig. 1). These two ECGs will be taken in the Emergency Department, the CCU, or the catheterization laboratory either just prior to cardiac catheterization or shortly thereafter. Both ECGs will be sent to a designated ECG reading center to be read and evaluated by five independent cardiologists, who are blinded to the initial clinical ECG readings, the type of ECG equipment used, and the patient’s clinical information. The five cardiologists will independently classify each ECG as either STEMI (anterior, inferior or posterior, and whether there is lateral involvement or not) or non-STEMI blinded to the clinical diagnosis. If all five reading cardiologists agree on the initial diagnosis of the ECG, that diagnosis becomes the official interpretation. However, if there is a discrepancy among the five readers’ diagnoses, they will consult with one another and reach a consensus diagnosis.

**Smartphone ECG system**

The AliveCor™ Heart Monitor is an FDA-approved Class II medical device that is a piece of peripheral hardware and can be attached onto the smartphone and wirelessly communicates with the smartphone (Fig. 1). AliveCor™ provides applications available for a broad range of smart devices, i.e. iPods, iPhones, and Android phones. The ECG is viewed via the downloaded app. No pairing between the smartphone and the Heart Monitor is required. Electrodes incorporated into the AliveCor™ Heart Monitor allows for wireless recording of 30-second rhythm strips to the app on the smartphone, and
potentially, simultaneously uploaded via cell or wi-fi connectivity to the cloud. ECGs can be downloaded for immediate interpretation using any web browser.

**ECG analysis**

A diagnosis of STEMI will be made when there is ST elevation at the J point in two contiguous leads with the cut points of $\geq 0.1$ mV (i.e., $\geq 1$ mm) in all leads other than V2–V3, where the cut points of $\geq 0.2$ mV ( $\geq 2$ mm) were used [17]. The definition of contiguous precordial leads is self-evident. Contiguity of frontal plane leads is defined based on the Cabrera orderly display (5 pairs of leads): aVL and I; I and −aVR (i.e., 1 mm ST depression in aVR is equivalent to 1 mm ST elevation in −aVR); −aVR and II; II and aVF; and, aVF and III [17].

In addition to the above STEMI criteria, the term ‘STEMI equivalent’ is used for $\geq 1$ mm ST segment depression in $\geq 8$ ECG leads plus $\geq 1$ mm ST segment elevation in lead aVR (or V1). Isolated ST segment depression of $\geq 1$ mm in contiguous leads V1–3 also is considered a STEMI equivalent for posterior myocardial infarction (i.e., generally due to isolated left circumflex occlusion).

Two ECG sets will be prepared for reading with two separate sets of ECGs: 1) a total set of randomly ordered standard and smartphone ECGs, and 2) a set of paired ECGs, i.e., each smartphone ECG presented with its standard ECG pair.

The grading form for the single ECG readings will contain the following entry columns: 1) the ID on the hard copy ECG; 2) the reader’s diagnosis of STEMI, Not STEMI, STEMI equivalent, left bundle branch block, or (technically) uninterpretable; 3) for STEMI diagnoses, whether the pattern shows an early acute, evolving, or chronic pattern; 4) columns for each of the 12 leads indicating whether ST-elevation meeting STEMI criteria (see above) is present (readers also have the option of providing quantification of ST-elevation in each diagnostic lead to within 0.5 mm); 5) whether the pattern suggests early repolarization (i.e., ‘looks abnormal but I think it is negative’); 6) whether there is a pattern that is non-diagnostic for STEMI, nevertheless presents a suspicious morphology (i.e., ‘looks possibly normal, but I think it may be positive’), or ‘I am not sure’; and 7) a miscellaneous comments’ column to allow for other items that the reader feels worth mentioning.

The grading form for the paired ECG readings contains the following entry columns: 1) the ID on the hard copy ECG; 2) a qualitative assessment as to whether the paired ECGs show good, fair, or poor correlation (i.e., whether all/ most, most/many, or few/none [or uninterpretable] leads show similar morphology, and whether the overall diagnostic categories are the same); 3) whether lead misplacement is suspected; and 4) a miscellaneous comments’ column to allow for other items that the reader felt worth mentioning.

**Statistical analysis**

Descriptive statistics will be used to report the operational assessments of the study, which include the time required for obtaining the smartphone ECG, “blinded” reading time, ease of obtaining the smartphone ECG, and any other obstacles encountered with the execution of the smartphone ECG. Differences, if any, between the smartphone ECG and standard ECG diagnoses will be reported. If disparities are noted, the chi-square statistic and the Fisher’s exact test may be used to evaluate differences based on diagnosis (STEMI vs. Non-STEMI).

Variables will be summarized as mean ± standard deviation and medians for continuous variables and frequencies for discrete variables. The chi-square statistic and Student t-test will be used to evaluate what patient characteristics were associated with differences in diagnoses. Using the 12–lead ECG as the gold standard, the sensitivity, specificity, positive predictive value and the negative predictive power will be calculated for the smartphone ECG. Because the sensitivity and specificity are equally important in determining the validity of the smartphone ECG, Youden’s J statistic will be calculated = sensitivity + specificity −1.0. The closer the value is to 1, the better the agreement is between the smartphone ECG and the 12–lead ECG.

To determine inter-rater agreement, the percent agreement will be calculated for both the standard 12–lead ECG and the smartphone ECG. Since some of the “agreements” by the readers may occur by chance, the kappa statistic will also be calculated which takes into account these chance occurrences when determining agreement. Frequencies will be calculated to determine the number of readings requiring a consensus consultation for each device. Subanalyses will be performed by age (<70 and >70), sex, and institution. All analyses will be performed using intention-to-treat. A $p$-value <0.05 will be designated as significant.

The combined marked improvements in smart device technology, its miniaturization (now hand-held), ready connectivity (cellular, wi-fi, etc.) and ubiquitous nature provide a platform to extend care and diagnostic capabilities for clinical decision and patient facing treatment support. The ability to obtain point-of-care 12-lead ECGs on smart devices owned by the general population that may be uploaded almost immediately to an accessible shared cloud-based server, provides an opportunity to change the way healthcare is delivered and provided. Local hospitals or healthcare systems as well as EMS services and communities may elect to create and subscribe to services that provide monitoring, alerts, and two-way communication to facilitate both access and speed of care. Technology is outpacing our current healthcare system approach, and this study will help to assess whether a smartphone obtained 12-lead ECG is an acceptable alternative to identify STEMI, which, if true, future study should assess the “sharing capabilities” of the smart device ECG and whether it can be used outside of the hospital setting by non-clinicians.

**Acknowledgments**

Funding: AliveCor™ provided the ECG devices used in this study. They have no role in the study design; in the collection, analysis and interpretation of data; in the writing of the paper; or in the decision to submit the article for
publication. All other funding is provided internally by the individual collaborating institutions.

Disclosures: David Albert is the founder and current chief medical officer of AliveCor, Inc. No other authors have conflicts of interest to disclose.

References


