Feasibility of combining serial smartphone single-lead electrocardiograms for the diagnosis of ST-elevation myocardial infarction☆

Joseph Boone Muhlestein, MD,[a,b] Jeffrey L. Anderson, MD,[a,b] Charles F. Bethea, MD,[g] Harry W. Severance, MD,[c,d] Robert J. Mentz, MD,[d] Gregory W. Barsness, MD,[f] Alejandro Barbagelata, MD,[h] David Albert, MD,[e] Viet T. Le, PA-C,[a,j] T. Jared Bunch, MD,[a,i] Frank Yanowitz, MD,[a,b] Heidi T. May, PhD,[a] Benjamin Chisum, BS,[a] Brianna S. Ronnow, MS,[a] and Joseph Brent Muhlestein, MD[a,b], for the Duke University Cooperative Cardiovascular Society (DUCCS) investigators

Abstract Background The rate-limiting step in STEMI diagnosis often is the availability of a 12-lead electrocardiogram (ECG) and its interpretation. The potential may exist to speed the availability of 12-lead ECG information by using commonly available mobile technologies. We sought to test whether combining serial smartphone single-lead ECGs to create a virtual 12-lead ECG can accurately diagnose STEMI.

Methods Consenting patients presenting with symptoms consistent with a possible STEMI had contemporaneous standard 12-lead and smartphone '12-lead equivalent' ECG (produced by electronically combining serial single-lead ECGs) recordings obtained. Matched ECGs were evaluated qualitatively and quantitatively by a panel of blinded readers and classified as STEMI/STEMI equivalent (LBBB), Not-STEMI, or uninterpretable. Interpretable ECG pairs were graded as showing good, fair, or poor correlation.

Results Two hundred four subjects (age = 60 years, males = 57%, STEMI activation = 45%) were enrolled from 5 international sites. Smartphone ECG quality was graded as good in 151 (74.0%), fair in 32 (15.7%), poor in 8 (3.9%), and uninterpretable in 13 (6.4%). A STEMI/STEMI equivalent diagnosis was identified by standard 12-lead ECG in 57/204 (27.9%) recordings. For all interpretable pairs of smartphone ECGs compared with standard ECGs (n = 190), the sensitivity, specificity, and positive and negative predictive values for STEMI/STEMI equivalent by smartphone were 0.89, 0.84, 0.70 and 0.95, respectively.

Conclusions A '12-lead equivalent' ECG obtained from multiple serial single-lead ECGs from a smartphone can identify STEMI with good correlation to a standard 12-lead ECG. This technology holds promise to improve outcomes in STEMI by enhancing the reach and speed of diagnosis and thereby early treatment. (Am Heart J 2020;221:125-135.)

ST-segment elevation myocardial infarction (STEMI) is a severe form of acute coronary syndrome with high morbidity and mortality if not diagnosed and treated quickly.[1] The diagnosis of STEMI is differentiated from other, often less severe forms of acute coronary syndrome by the presence of ST segment elevation on a 12-lead electrocardiogram (ECG).[2] Obtaining this important information quickly is essential in initiating appropriate and timely triage and treatment.[3, 4] Despite the proliferation of ECG equipment in many modern healthcare settings, there remain many locations where this test is not easily accessible, such as in rural and remote locations, airplanes, cruise ships, hotels, homes, and many underdeveloped regions of the world. An inexpensive, portable, readily available ECG system, capable of diagnosing STEMI, may improve outcomes in these currently underserved environments. Such technology may also improve triage for high-risk individuals in more developed areas.

From the [a]Intermountain Medical Center, Intermountain Heart Institute, Salt Lake City, Utah, [b]University of Utah, Department of Internal Medicine, Salt Lake City, Utah, [c]Erlanger Institute for Clinical Research, UT College of Medicine, Chattanooga, Tennessee, [d]Duke University, Durham, North Carolina, [e]AliveCor™ Corporation, San Franscisco, California, [f]Mayo Clinic, Rochester, Minnesota, [g]Integris Heart Hospital, Oklahoma City, Oklahoma, [h]Catholic University Buenos Aires, Argentina, [i]Stanford University, Department of Internal Medicine, Palo Alto, California, and [j]Rocky Mountain University of Health Professions, Masters of Physician Assistant Studies Program, Provo, Utah.

☆Declarations of Interest: None

Submitted September 27, 2019; accepted December 21, 2019.

Reprint requests: Joseph Brent Muhlestein, MD, Intermountain Heart Institute, 5121 South Cottonwood St, Salt Lake City, Utah 84107.
E-mail: JBrent.Muhlestein@imail.org

0002-8703

https://doi.org/10.1016/j.ahj.2019.12.016

The proliferation of smartphone technology has made available a platform that may extend the availability of ECG recordings. Smartphones are handheld computing devices characterized by having the capability to access the internet and including an operating system capable of running installed applications. Smart devices such as many tablet computers and media players are similar but lack the ability to make voice calls, although they run comparable operating systems and may have the ability to access the internet. For practical purposes, these terms are often used interchangeably and will be referred to collectively as smartphones herein. Smartphones have become ubiquitous, with over 2.1 billion smartphone users as of 2016, and with numbers continuing to climb rapidly in both developed and underdeveloped countries.[5]

The availability of powerful mobile computers has led to the ability to run many highly sophisticated applications or 'apps'. This ability makes possible specialized applications that work with a small separate sensor to provide single channel ECG rhythm recordings. One such app and sensor combination has been shown to be effective in detecting rhythm abnormalities such as atrial fibrillation.[6-8] In diagnosing atrial fibrillation, blinded comparisons of smartphone-based rhythm strips, by interpreting cardiologists and automated algorithms, have shown sensitivities from 87% to 100% and specificities from 90% to 97% with overall accuracies from 90% to 97% when compared to 12-lead ECGs.[9] Similar functionality also has been incorporated into a new wearable device, the Apple Watch Series 4, which was recently introduced to the market as an FDA cleared class II medical device.[10]

Thus far, smartphone-based electrocardiography has been used primarily for rhythm analysis. The reason for this is largely technical, as a single-lead rhythm strip requires only two sensors, which are easily embedded in a case.[7] In contrast, a typical 12-lead ECG requires 9 electrodes to be placed on the limbs and chest.[11] One solution to this challenge, and which requires only 2 electrodes on the smartphone-associated sensor, is to use sequential single-lead ECG measurements that are then electronically averaged and shown as a single representative tracing called a '12-lead ECG equivalent'. A test device has been made that works on this principle and is based on the AliveCor™ Heart Monitor (Figure 1). The technical differences between a 12-lead equivalent ECG tracing and a traditional 12-lead ECG are detailed in Table I. In brief, it presents serial data measurements as averaged beats rather than raw voltage data, requires vector summation of multiple tracings, and uses a single limb lead as the ground for the precordial leads. However, how well such a 12-lead equivalent ECG compares to a standard 12-lead ECG, especially in relation to diagnosing STEMI is not known.

A pilot study testing the operational feasibility of obtaining a 12-lead equivalent ECG in patients with STEMI was recently reported.[12] This pilot study showed that it was possible to obtain 12-lead equivalent ECGs with commonly available smartphone technology. That study also showed promising correlations to standard 12-lead ECGs. It also demonstrated some of the operational difficulty in using the current device to obtain useable tracings. Based on the experience learned from the pilot study, a large trial was therefore designed and conducted, the results of which we now report.

Methods

Trial design

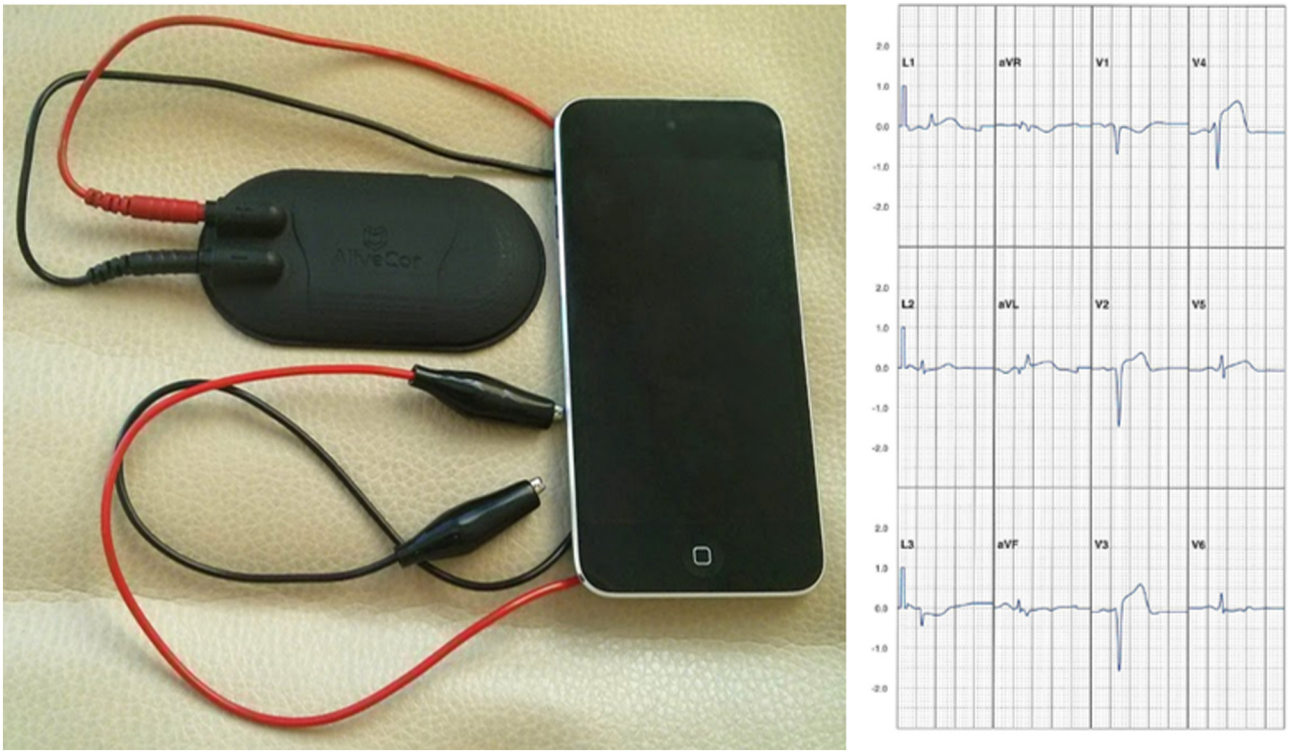
The *Smartphone ECG for Evaluation of ST-Segment Elevation Myocardial Infarction Study* (ST LEUIS) trial was a multicenter, international, prospective, nonrandomized, open trial with each patient serving as his or her own control. ST LEUIS is registered at clinicaltrials.gov as number NCT02498405. The details of the trial design have been previously published.[13] Briefly, a total of five different institutions associated with the Duke University Cooperative Cardiovascular Society (DUCCS) organization participated in the trial. Each site obtained approval from their individual Institutional Review Boards. Informed consent was obtained for all patients prior to enrollment. Two distinct patient populations were investigated. The first population included patients for which the STEMI protocol had been activated. The second population was broader, including any patient presenting to the emergency department with chest pain. Inclusion and exclusion criteria are detailed in Online Table I. Baseline characteristics for each patient were collected, including age, gender, subjective grade of chest pain (typical or atypical), and location where tracings were obtained.

The device used for this study was a modified version of the AliveCor™ Heart Monitor, an FDA-approved Class II medical device, paired with a 5th generation iPod Touch device (see Figure 1). This modified device has two electrical leads connected to wires with alligator clips, which are then attached to the same adhesive stickers used in the standard 12-lead ECG. This is the same device used previously in the pilot study.[12]

The tracings for the first population, in which the STEMI protocol had been activated, were obtained at the earliest possible opportunity that did not interfere with patient care. This could have been in the emergency department, in the catheterization laboratory, or in the coronary care unit within 1 hour following the angiographic procedure. Tracings for the second population, in which there was no activation of the STEMI protocol, were performed in the emergency department.

The initial step in the process of collecting ECGs was to obtain a standard 12-lead ECG. The smartphone device was then connected to the same stickers and used to

Figure 1



AliveCor ™ Heart Monitor and Representative '12-lead ECG equivalent'. Left figure: The AliveCor ™ Heart Monitor, with two alligator clips, linked to a 5th generation iPod Touch. This is one of the devices used in the trial. Right figure: Representative '12-lead ECG equivalent' showing acute anterior MI.

collect 9 sequential tracings of at least 10 seconds each. Leaving the same ECG stickers used in the standard 12-lead ECG in place for use in the smartphone 12-lead equivalent ECG was done to eliminate variation based on lead placement. Details of lead placement are shown in Figure 2. For leads V1-V2, the left arm lead was used as ground; for V3-V6, the right arm lead was used as ground. The obtained smartphone tracings were uploaded wirelessly for processing remotely (see Online Figure 1). The augmented limb leads were obtained via vector summation of leads L1, L2 and L3 (as shown in Figure 2) during post processing. The 12-lead equivalent ECG could then be accessed immediately via the internet.

ECG analysis

A subjective evaluation of the technical quality (graded as good, fair, poor, or unreadable) of all smartphone ECGs was performed by a single investigator. For comparison of the standard 12-lead and smartphone ECGs, tracings from both groups were combined to create a single cohort with an adequate number of ECGs both with and without evidence of STEMI.

Two ECG sets were created. The first set included all tracings (12-lead ECGs and smartphone 12-lead equivalent ECGs) in a random order with no ordered connection between tracings from the same patient. The second set included all the same tracings but with tracings from the same patient displayed in juxtaposition. Both sets were interpreted in a blinded fashion by an expert reading co-author panel of 5 cardiologists. It should be noted that, although all ECGs were blinded, the standard 12-lead and smartphone 12-lead equivalent ECGs could be easily distinguished because of the differences in their tracing formats.

For the first ECG set, the reading panel was instructed to designate each independent ECG as STEMI/left bundle branch block (LBBB)/'STEMI equivalent', 'Not-STEMI', or uninterpretable, according to accepted guidelines for the standardization of interpretation of ECGs.[14] STEMI was defined as ST-segment elevation of at least 1 mm (0.1 mV) in any 2 adjacent leads except V2 and V3, which required at least 2 mm ST elevation, the simplification in this criterion due to the reading panel being blinded to patient age and gender. LBBB with chest pain was regarded as a STEMI equivalent. This definition, as well as additional grading criteria, are detailed further in the previously published study design manuscript.[13] For the second set, the juxtaposed ECGs were subjectively

Table I. Technical differences between the smartphone '12-lead equivalent' ECG, obtained using only two electrode sensors, and a traditional 12-lead ECG.

1. The smartphone technique requires sequential measurements to be made, which produces tracings that are contemporaneous but non-simultaneous.
2. Augmented limb leads are a computer averaged summation of multiple tracings.
3. Precordial leads are obtained using a single limb lead for ground.
4. All tracings are presented as an averaged tracing, so no raw signal data are preserved. To minimize the potential for morphological corruption by signal averaging, computer algorithms are employed to exclude premature ventricular complexes from the averaging process.

assessed to have good, fair, or poor correlation in tracing morphology.

Following initial interpretation of the un-matched ECGs, any discrepant interpretations were adjudicated by discussion among the reading panel until a consensus was reached. The interpreted ECGs were then re-matched by patient, and the presence of discordant reads between the two ECG modalities was identified. Quantitative analysis of ST segments was performed on all discordant ECG sets by a single member of the reading panel, and the average difference in ST segment deviation was quantified.

Trial objectives

The primary objective of this trial was to determine whether the 12-lead equivalent ECG obtained via smartphone is an acceptable equivalent to a standard 12-lead ECG in diagnosing or excluding STEMI. To evaluate this objective, the following specific aims were proposed:

1. Obtain contemporaneous recordings of a standard 12-lead ECG and smartphone 12-lead equivalent ECG on patients presenting with chest pain for which the STEMI protocol was activated and also on patients presenting to the emergency department for evaluation of chest pain but not necessarily presenting with STEMI.
2. 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 was a possibility.
3. Determine the sensitivity, specificity, and positive and negative predictive values of the smartphone 12–lead equivalent ECG using a paired contemporaneous standard 12–lead ECG as the gold standard.

Statistical analysis

Variables were summarized as mean ± standard deviation (SD) for continuous variables and frequencies for discrete variables. The Pearson's chi-square test was used to determine significant differences between subgroups for non-interpretable vs. interpretable and equivalent vs. discrepant tracings. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for STEMI/LBBB and Not-STEMI. Two-tailed p-values are presented with 0.05 designated as nominally significant.

Results

Baseline demographics of the trial cohort

The trial cohort was comprised of 204 patients evaluated for chest pain to assess for STEMI at the 5 participating medical centers (Table II). Age averaged 59.8 ± 15.7 years (median 60; range, 21 to 95), and 56.9% were male. Chest discomfort was rated as typical for ischemia in 121 (59.3%), atypical in 81 (39.7%), and was unknown in 2 patients (1.0%). A total of 92 (45.1%) patients, for whom the STEMI protocol was activated, and 112 (54.9%) patients who presented to the emergency department for evaluation of acute chest pain, were enrolled. Paired study ECGs were obtained in the following locations: emergency departments in 104 (51.0%), catheterization laboratory pre-procedure in 2 (1.0%), catheterization laboratory post-procedure in 41 (20.0%), the coronary intensive care unit (CICU) in 56 (27.5%), and unknown in 1 (0.5%),

Smartphone ECG technical quality

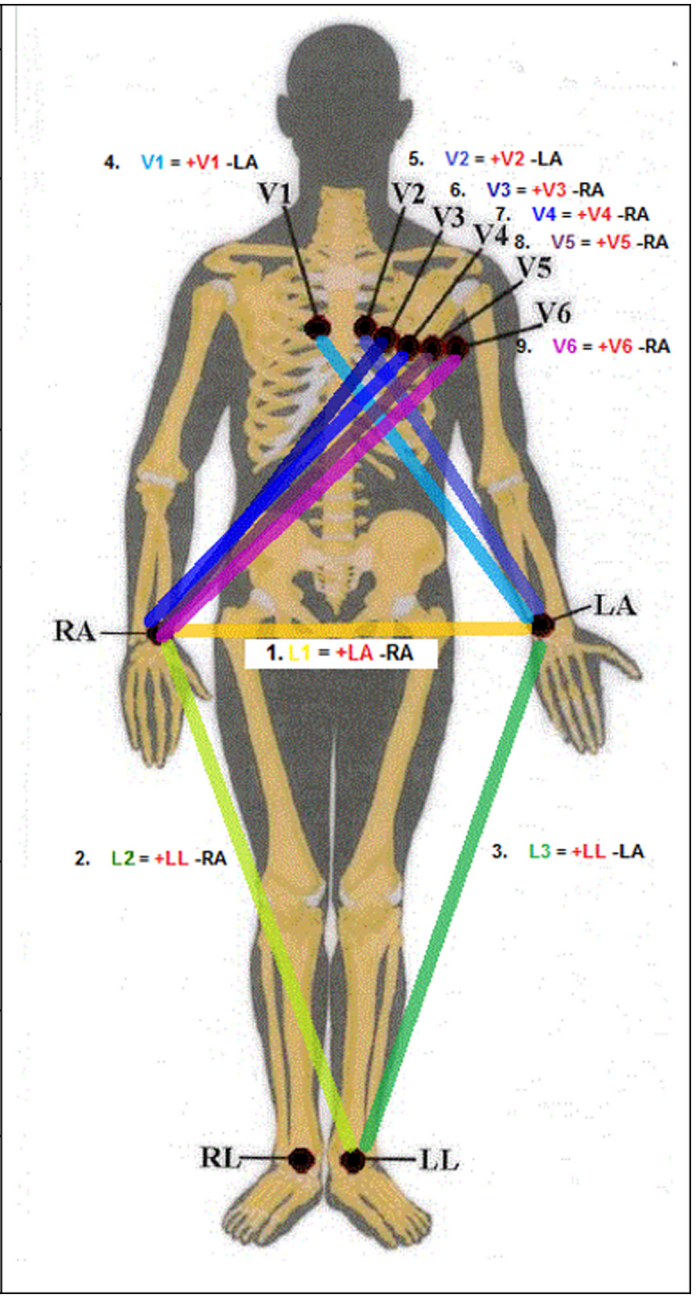
ECG technical quality was graded as good or fair in 183 (89.7%) and poor or unreadable in 21 (10.3%) of the 204 smartphone tracings (Online Table II). Technical quality differed significantly between high and low enrolling sites: 10/40 (25%) ECGs were uninterpretable among those obtained in the 2 lowest enrolling sites (n = 13 and n = 27 patients) compared to only 3/164 (1.8%) for the 3 highest enrolling sites (n = 50, n = 52 and n = 62 patients; $P < .0001$). The distribution of fair/poor ECGs was 14/40 (35.0%) for low enrolling sites and 26/164 (15.9%) for high enrolling sites ($P < .0001$). The lowest enrolling site (n = 13) was a quality outlier. Excluding this site, respective ECG quality metrics of the other 191 smartphone ECGs were: good or fair in 179 (93.7%) and poor or uninterpretable in 12 (6.3%).

Comparisons between standard 12-lead and smartphone ECG diagnostic interpretations

Preliminary reading panel ECG diagnosis adjudication resulted in full initial agreement between the 5 panel members in 285 (70%) of the 408 available ECGs (Table III, Table IV). Thereafter, panel discussion to reach an interpretive consensus was required for 45 (22.1%) of the 12-lead and 78 (38.2%) of the smartphone ECGs. Using the 'gold-standard' 12-lead ECGs, the diagnosis of STEMI was made in 46 (22.5%), LBBB in 11 (5.4%), Not-

Figure 2

LEAD	Positive	Negative
L1	+LA	– RA
L2	+LL	– RA
L3	+LL	– LA
V1	+V1	– LA
V2	+V2	– LA
V3	+V3	– RA
V4	+V4	– RA
V5	+V5	– RA
V6	+V6	– RA



Anatomic diagram of lead placement locations for sequential ECG measurements. Augmented limb leads were obtained, via post-processing, using leads L1, L2 and L3 according to the formulas: Lead aVR = (–L1 – L2)/2; Lead aVL = L1 – (L2/2); Lead aVF = L2 – (L1/2). LA = Left arm; RA = Right arm; LL = Left leg.

STEMI in 146 (71.6%), and uninterpretable in 1 (0.5%), which was due to ventricular pacing (Table II). Corresponding diagnoses by smartphone ECG were: STEMI in 60 (29.4%), LBBB in 11 (5.4%) (3 [1.5%] also had qualifying ST-elevation for STEMI and 8 [3.9%] did not), Not-STEMI in 120 (58.8%), and uninterpretable in 13 (6.4%).

Blinded, separate readings of interpretable smartphone and 12-lead ECG pairs resulted in the same/equivalent diagnosis (STEMI/STEMI equivalent/LBBB [with or

Table II. Patient characteristics, overall, and stratified by whether the STEMI protocol was activated or not activated. All characteristics between the STEMI and not STEMI protocol activation were significantly different (all $P \leq .002$).

	Overall, n = 204	Chest pain, with STEMI protocol activation, n = 92	Chest pain, with STEMI protocol not activated, n = 112
Age (years)			
Mean ± SD	59.8 ± 15.7	65.6 ± 13.2	55.0 ± 16.0
Median (range)	60 (21–95)	64.5 (32–92)	55.0 (21–86)
Gender			
Female	88 (43%)	29 (32%)	59 (53%)
Male	116 (57%)	63 (68%)	53 (47%)
Presenting chest pain type			
Typical	121 (59%)	78 (85%)	43 (38%)
Atypical	81 (40%)	12 (13%)	69 (62%)
Unknown	2 (1%)	2 (2%)	0 (0%)
Location of ECG			
Cath lab after procedure	41 (20%)	40 (43%)	1 (1%)
Cath lab before procedure	2 (1%)	1 (1%)	1 (1%)
Emergency department	104 (51%)	3 (3%)	101 (90%)
CICU	56 (27%)	47 (51%)	9 (8%)
Unknown	1 (1%)	1 (1%)	0 (0%)

STEMI, ST-segment elevation myocardial infarction; SD, standard deviation; ECG, electrocardiogram; CICU, coronary intensive care unit.

without STEMI qualifying ST-elevation], or Not-STEMI) in 163 of 190 pairs (85.8%) (see Table IV). Subsequent, unblinded side-by-side comparison suggested diagnostic equivalency in an additional 4 (2.1%) pairs, increasing diagnostic accuracy to 87.9%. Technically suboptimal but still interpretable smartphone recordings were present in 5 of the paired, discrepant reading comparisons, representing 2.6% of interpretable paired recordings. The 18 remaining discrepancies (9.5% of interpretable paired readings) were explained by small voltage differences in ST-segment elevation, which met criteria for STEMI in one but not the other ECG; these differences led to a STEMI diagnosis by smartphone but not 12-lead ECG in 15 pairs and by 12-lead but not smartphone ECG in 3 pairs. The average difference in ST elevation in diagnostic leads between discrepant diagnostic pairs was generally <1 mm (<0.1 mV; mean difference, 0.09 mV).

Table III. The distribution of diagnoses among the 12-lead ECG and smartphone ECG.

Diagnosis	12-lead ECG	Smartphone ECG
STEMI (all 204 patients)	46 (23%)	60 (29%)
–STEMI with STEMI protocol activation	41 (22%)	43 (21%)
–STEMI without STEMI protocol activation	5 (3%)	17 (8%)
LBBB (all 204 patients)	11 (5%)	11 (5%)
–Without qualifying ST elevation	11 (5%)	8 (4%)
–With qualifying ST elevation	–	3 (1%)
Not-STEMI	146 (72%)	120 (59%)
Not interpretable	1 (1%)*	13 (6%)

ECG, electrocardiogram; STEMI, ST-segment elevation myocardial infarction; LBBB, left bundle branch block.
*Due to ventricular pacing during 12-lead ECG acquisition.

Side-by-side comparisons between standard 12-lead and smartphone ECG pairs

The reading panel consensus correlations between interpretable side-by-side smartphone and 12-lead ECGs (n = 190 pairs) were considered good in 166 (87.4%) (see Figures 3 and 4 and Online Figure 2), fair in 23 (12.0%) (see Online Figure 3), and poor in 1 (0.5%). Side-by-side comparisons were not attempted in the remaining 14 pairs because of unreadable technical quality (see Online Figure 4) in the smartphone ECGs (n = 13) or because of ventricular pacing in the 12-lead ECG (n = 1).

Subgroup analyses of paired comparisons

Key subgroups were analyzed for the proportion with interpretable smartphone ECGs and, within each subgroup, of those with equivalent (versus discrepant) diagnoses (compared with the 12-lead ECG) (Online Table III). Successful performance of an interpretable smartphone ECG was not affected by patient gender or age, whereas success did vary by location (with the CICU being a poorly performing location) and by study site (with low-recruiting site 5 being an outlier). There was no significant heterogeneity among interpretable ECG pairs in achieving a diagnosis equivalent to the 12-lead ECG among these 4 subgroups (accounting for multiplicity of testing).

Sensitivity and specificity for ECG diagnoses by smartphone ECG

The sensitivity, specificity, positive, and negative predictive values based on blinded, consensus ECG diagnoses of STEMI/LBBB and Not-STEMI for interpretable pairs are shown in Table V. Of note are the high sensitivity and negative predictive values for STEMI/LBBB and the very high specificity and positive predictive values for Not-STEMI (i.e., 89–95%). Of the 23 interpretable but discrepant diagnostic pairs noted above, the smartphone ECG missed a 12-lead ECG STEMI/STEMI

Table IV. The number of similar and different diagnoses between the smartphone and 12-lead ECG.

	12 lead: STEMI/LBBB	12 lead: Not-STEMI	Total
Smartphone: STEMI/LBBB	49	21	70
Smartphone: Not-STEMI	6	114	120
Total	55	135	190

equivalent call in only 4, which was due to minor voltage differences (in 3) or a wandering baseline and missing leads (in 1). In 2 of the 3 recordings of good smartphone quality, the smartphone clearly indicated an evolving Q-wave inferior or anteroseptal MI (though not meeting the definition for 'acute'), and in the third, early repolarization was a more likely cause of ST-elevation in the 12-lead ECG than true STEMI. In 18 of the other discrepant pairs, the discrepancy was explained by small voltage differences in ST segment elevation, which just met criteria for STEMI in one but not the other ECG. These observations suggest that, in most circumstances, a technically adequate smartphone ECG is capable of effectively identifying true acute and evolving STEMI and STEMI equivalent diagnoses as identified by the 12-lead 'gold standard' ECG.

Discussion

Key trial findings

This trial represents the first large-scale evaluation of the feasibility of using serial single-lead ECGs obtained from a portable smartphone-based technology to detect STEMI in acute chest pain patients. It demonstrates that clinically interpretable tracings for the diagnosis of STEMI can be obtained using a commonly available smartphone platform with good correlation to the standard 12-lead ECG. When performed technically correctly, correlation improves such that the smartphone ECG can identify essentially all true acute/evolving STEMI/STEMI equivalent diagnoses indicated by the 12-lead 'gold standard' ECG. The disparity noted in this trial between the high and low enrolling sites in successfully obtaining good quality smartphone ECGs demonstrates that experience and local expertise are necessary to successfully obtain technically adequate smartphone ECGs using our presently available simple modifications to the standard single-lead smartphone ECG devices. However, now that the feasibility of successfully diagnosing acute STEMI has been demonstrated, technical improvements to the device can be accomplished that will make its application more user-friendly and accurate.

The subjective aspect of all ECG interpretation, especially when dealing with morphologic characteristics, was made apparent in this trial. Despite the use of expert cardiologists, there was far from complete diagnostic agreement among the five reading panel members in a quarter to a third of both 12-lead and smartphone tracings, which required consensus adjudication. However, the overall discrepancy rate *between* the 2 modalities was much lower (13.2%). In most cases, discrepancies among readers related to borderline ST-segment elevations or technical problems with the recordings.

Comparison to prior studies

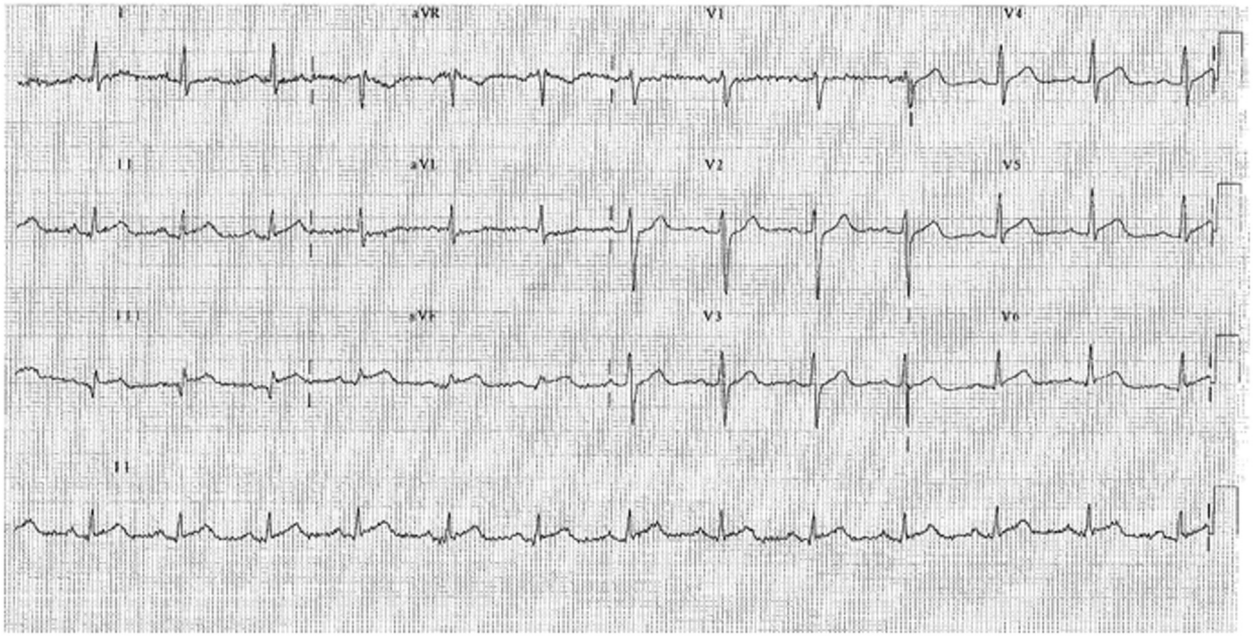
This trial represents a unique avenue of investigation, with no previous trial of comparable extent present in the reviewed literature. The only prior study evaluating the diagnosis of STEMI with smartphone-based ECG recordings was the pilot study published by the present authors.[12] The present trial differs compared to the pilot study by its choice of a single precordial grounding technique, the inclusion of chest pain patients without a STEMI protocol activation, participation of multiple international centers, and a much larger patient population. Additionally, it employed blinded (as well as unblinded) ECG interpretations and comparisons. However, the hardware and software used were identical in the present trial and the pilot study.

Technical considerations

As described in Table I, the techniques used to produce smartphone '12-lead equivalent' ECGs differed in at least four specific ways from those used to produce standard 12-lead ECGs. Each of these technical differences has the potential to introduce variation between the two ECG modalities. However, this trial demonstrated that, when acquisition of the smartphone ECG was performed correctly, these technical differences resulted in only modest morphologic changes in comparison to the matching standard 12-lead ECG. There was concern that the signal averaging performed by the smartphone system, and its resultant loss of the ability to see the raw data (point 4 in Table I), may be a source of error. Averaged tracings make it difficult to determine how much the synthesized beat was influenced by noise or ectopic beats such as PVCs or paced beats. However, in the present trial, this did not prove to be a significant problem, presumably because there were few instances of ectopic beat interference or because the basic PVC elimination algorithm used in the software worked adequately.

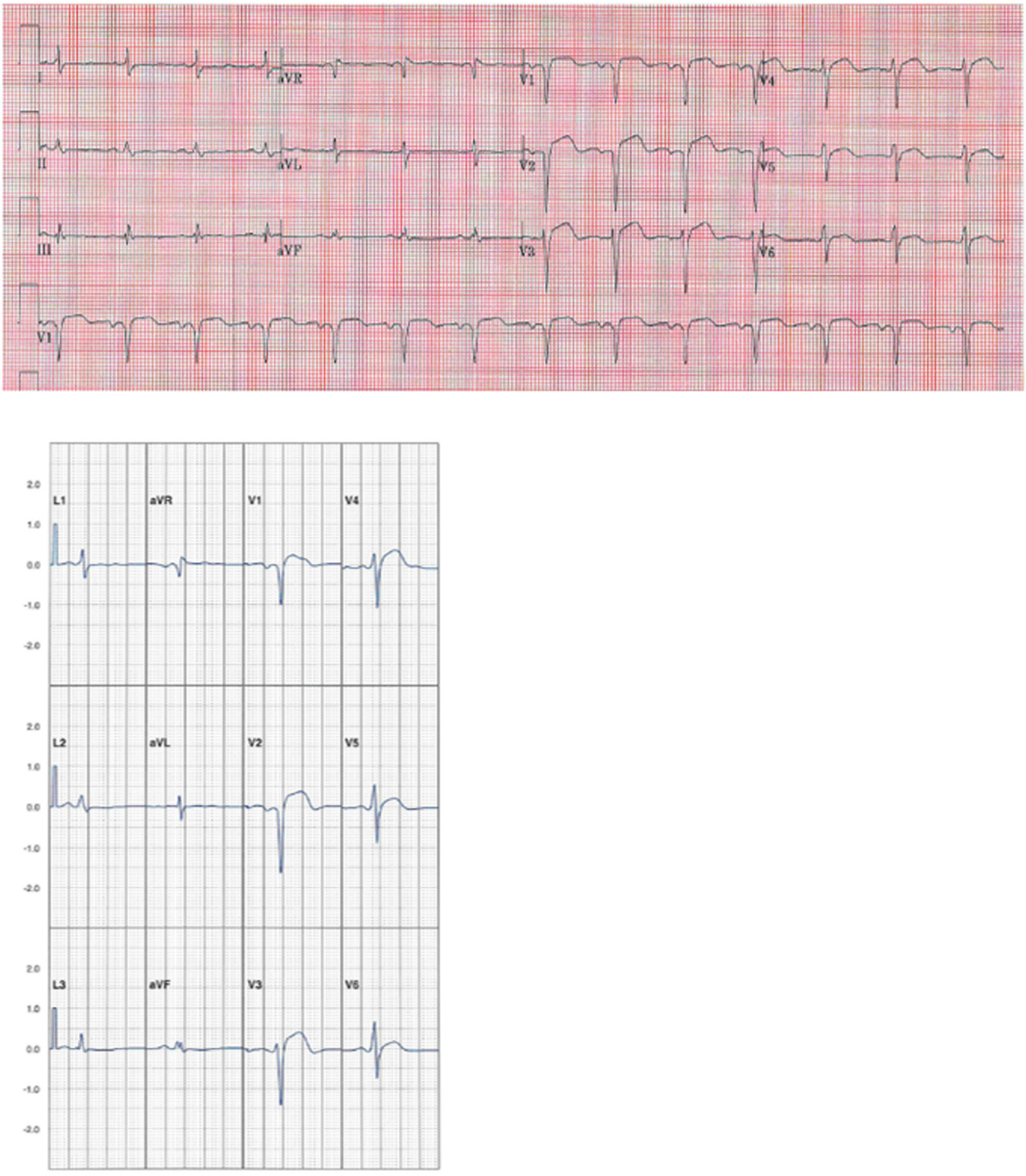
Applying the manual techniques used in this trial to consistently produce a high-quality smartphone '12-lead equivalent' ECG proved to be a more significant challenge. A total of 9 separate ECG tracings were required for each smartphone 12-lead equivalent ECG, and each had to be acquired in a specific order and pattern, with proper lead changes between each tracing.

Figure 3



Inferior wall myocardial infarction matched ECG pair. Standard 12-lead ECG and smartphone ECG matched pair adjudicated as showing inferior wall myocardial infarction with good correlation.

Figure 4



Acute anterior wall myocardial infarction matched ECG pair. Standard 12-lead ECG and smartphone ECG matched pair adjudicated as showing acute anterior wall myocardial infarction with good correlation.

This resulted in significant variations among the sites, based on the local experience and training of the operators. This observation emphasizes a need to simplify the technique before considering widespread adoption of the smartphone ECG system into less trained and controlled environments. A solution that is expected to

Table V. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the smartphone ECG for a STEMI/LBBB and not-STEMI diagnosis.

	Sensitivity	Specificity	PPV	NPV
STEMI/LBBB	0.89	0.84	0.70	0.95
Not-STEMI	0.84	0.89	0.95	0.70

STEMI, ST-segment elevation myocardial infarction; LBBB, left bundle branch block.

reduce potential technical variation, and is simpler to use, has now been developed. In this newer version, a third lead has been added, which allows for simultaneous recordings of all limb leads by having a lead connected to each arm and to the left leg. Therefore, the only sequential tracings that will be required are the six precordial leads, which can be obtained by leaving the two arm leads in place and moving the lead previously attached to the left leg across the precordium and taking measurements at each precordial location. This system should eliminate many of the disadvantages listed in points 2 and 4 in Table I. Having both arms serve as ground also should improve point 3 and make it unnecessary to switch grounding leads across the precordium. While adding a third ECG lead still accomplishes the goal of maintaining relatively simple hardware suitable for a portable, smartphone-based system, the increased technical simplicity in obtaining the 12-lead equivalent ECG tracing with this change should make the entire process faster and more error-free. A prototype of this proposed system developed by AliveCor™ is shown in Online Figure 5.

Producing a more complete and refined smartphone computer application to support the proposed hardware should further improve the quality of the tracings obtained. Tracings in this study were made using paper instructions at the patient's side with no feedback regarding the quality of tracings or whether leads were in the proper position. Creating an application with coaching functionality for lead placement and with the diagnostic ability to identify technical errors such as lead reversal, excessive noise, and poor signal strength, should further improve tracing reliability and decrease the training needed to obtain high quality smartphone ECG tracings. Indeed, a computerized ECG interpretation function that provides to the person performing the smartphone ECG a near instantaneous diagnosis of STEMI versus Not-STEMI and recommendations as to how to proceed in the care of the patient could be added easily. Such functionality should be helpful in providing rapid and appropriate care to possible STEMI patients in the field.

Trial strengths and limitations

Some important strengths of the current trial include its moderately large number of enrolled patients, the use of the same ECG lead stickers for both ECGs to avoid lead placement variation, and the close time proximity between the obtained ECG tracings for both modalities. Also, multiple trial sites, with a broad geographic distribution, were employed. This allowed for excellent testing of the generalizability of the proposed system. Another strength was that a blinded panel of expert ECG readers was used for interpretation and adjudication of the key trial results.

Limitations of the present trial include the fact that, while the matched ECG tracings obtained were contemporaneous, they were not simultaneous. Thus, evolution of the ECG signal between tracings could have occurred. However, the time differential between matched tracings was rarely more than 5 minutes. Also, we focused on the potential diagnosis of STEMI to the exclusion of other ECG changes. The use of strict, pre-defined definitions left many clinically relevant nuances of the tracings unaccounted for. For example, distinguishing early repolarization ST-elevation from a true STEMI pattern was not considered. Further, ischemic changes such as ST-depression or T-wave inversion were also not systematically graded and recorded, despite their presence in many tracings from both modalities and their relevance to the diagnosis of acute coronary syndromes. Additionally, the use of a highly selected population for STEMI may have led to an increased positive predictive value compared to a less selected population.

Finally, we used trained clinical researchers in controlled hospital environments to obtain our smartphone tracings, whereas the primary goal of developing smartphone ECG technology is that it be used outside of general clinical practice in the real-world environment. Now that feasibility has been demonstrated, further real-world studies will be needed.

Conclusions

This first-of-its-kind multicenter study demonstrates that a 12-lead equivalent ECG obtained by combining serial single-lead ECGs using a smartphone coupled to a software application and an inexpensive 2-wire attachment can identify STEMI vs Not-STEMI diagnoses with good correlation with the standard 12-lead ECG. This technology holds substantial promise for the future diagnosis and management of patients experiencing STEMI by enabling more rapid diagnosis and treatment, leading to improved outcomes. Further refinement of system software and hardware should further improve on these results and broaden clinical application to many common real-world scenarios through increased ease-of-use and reliability.

Acknowledgements

We appreciate Claudia Bruno, MD, of Clinica Zabala for assistance with the ECGs collected there.

Funding

AliveCor™ (San Francisco, California) graciously provided the ECG devices used in this study as well as a laptop with Matlab software pre-installed. All equipment was returned to AliveCor™ on completion of the trial. AliveCor™ had 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 was provided internally by the individual collaborating institutions.

In Memoriam

It is with great honor, love and respect that we publish this manuscript in memory of the late Professor Galen S. Wagner, MD, PhD (1939-2016)—our mentor, colleague and friend. Dr. Wagner was the founder of the Duke University Cooperative Cardiovascular Society (DUCCS) and the primary driver for the initiation of the ST LEUIS trial. Until his death, he was the editor of the Journal of Electrocardiology and will ever be remembered for his love of ECGs.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.12.016.

References

1. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017;376:2053-64.
2. Anderson JL. ST-elevation acute myocardial infarction and complications of myocardial infarction. In: Goldman L, Schafer AI, eds. Goldman's Cecil Medicine. 25th edition. Philadelphia, Pennsylvania: Elsevier Saunders; 2016441-56.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.
4. Goff Jr DC, Feldman HA, McGovern PG, et al. Prehospital delay in patients hospitalized with heart attack symptoms in the United States: the REACT trial. Am Heart J 1999;138:1046-57.
5. Number of smartphone users worldwide 2014–2020. Statista. [Online]. Available at: , https://www.statista.com/statistics/330695/number-of-smartphone-users-worldwide/. Accessed May 4, 2018.
6. Saxon LA, Smith A, Doshi S, et al. iPhone rhythm strip–The implications of wireless and ubiquitious heart rate monitoring. J Am Coll Cardiol 2012;59, E726.
7. Garabelli P. Accuracy and novelty of an inexpensive iPhone-based event recorder. Presented at the Heart Rhythm 33rd Annual Scientific Sessions, Boston, MA, May 2012.
8. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor Heart Monitor to screen for atrial fibrillation: The REHEARSE-AF Study. Circulation 2017;136:1784-94.
9. Lau JK, Lowres N, Neubeck L, et al. iPhone ECG application for community screening to detect silent atrial fibrillation: A novel technology to prevent stroke. Int J Cardiol 2013;165:193-4.
10. Fingas R. Apple Watch Series 4 EKG tech got FDA clearance less than 24 hours before reveal. *AppleInsider*, 08-Sep-2018. [Online]. Available at: , https://appleinsider.com/articles/18/09/18/apple-watch-series-4-ekg-tech-got-fda-clearance-less-than-24-hours-before-reveal. Accessed October 16, 2018.
11. ECG Learning Center - An introduction to clinical electrocardiography. [Online]. Available at: , https://ecg.utah.edu/lesson/1. Accessed May 17, 2018.
12. Muhlestein JB, Le V, Albert D, et al. Smartphone ECG for evaluation of STEMI: Results of the ST LEUIS Pilot Study. J Electrocardiol 2015;48:249-59.
13. Barbagelata A, Bethea CF, Severance HW, et al. Smartphone ECG for evaluation of ST-segment elevation myocardial infarction (STEMI): Design of the ST LEUIS International Multicenter Study. J Electrocardiol 2018;51:260-4.
14. Wagner GS, Macfarlane P, Wellens H, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part VI: acute ischemia/infarction: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53:1003-111.