Optimizing Pre-Hospital Electrocardiography to Improve the Early Diagnosis of Acute Coronary Syndrome

by

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Dedication

I dedicate this work to my beloved Mr. Albert Gribble, who joined our family when I began graduate studies in the master's program, and passed gracefully by my side at the completion of this doctoral dissertation.

Thank you for accompanying me on this journey from start to finish.

You will forever be missed and loved beyond words.

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Abstract

Myocardial ischemia is dynamic and unpredictable which, if not identified and treated promptly, can lead to devastating outcomes. Pre-hospital electrocardiography may facilitate early intervention by identifying patients with acute coronary syndrome (ACS) promptly. The goal of this dissertation research was to determine the prevalence and clinical significance of electrocardiographic (ECG) abnormalities of ischemia that occur in the pre-hospital setting in patients who contact '911' for chest pain and other anginal equivalent symptoms. While previous investigations have examined the impact of a snapshot 12-lead pre-hospital ECG (PH ECG), this study is the first to analyze ST-segment monitoring triggered 12-lead ECGs that have been acquired in the pre-hospital setting. The diagnostic and prognostic capabilities of PH ECG in the management of ACS have been examined and described.

The first paper is a critical literature review of the scientific literature about pre-hospital electrocardiography. Several themes that emerged from the literature and form the bases of this paper include: clinical effects of PH ECG (timing, roles, effects on patient outcome and characteristics of patients with PH ECG), diagnostic performance, and prognostic/predictive value of PH ECG.

The second paper is a secondary analysis of data from patients (n=620) who activated '911' for chest pain symptoms to determine the sensitivity and specificity of 12-

lead ECG ST-segment monitoring in the pre-hospital period for diagnosing acute ACS. Both the PH ECG and the initial hospital ECG data for each patient were included in this study. The sensitivity of the ECG for diagnosing ACS was significantly improved when used in conjunction with the initial hospital ECG.

The third paper is a secondary analysis of data from the same cohort as previously described above, but includes only the PH ECG data for each patient (n=630). The purpose of the study was to determine whether manifestations of acute myocardial ischemia on the PH ECG are predictive of adverse hospital outcomes. Patients with evidence of PH ECG ischemia had a significantly higher proportion of adverse hospital outcomes than those without PH ECG ischemia. Furthermore, PH ECG ischemia was found to be an independent predictor of adverse hospital outcomes.

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Chapter 1

Introduction

Background

Coronary heart disease (CHD) is the leading cause of death in the United States (U.S.) (Thom, 2006) and nearly 17 million persons in the U.S. are currently diagnosed with it (American Heart Association, 2009). The incidence of cardiovascular disease in the U.S. increased rapidly during the last century and currently claims the lives of nearly one million people annually (Banasik, 2005). CHD caused one of every five deaths in the United States (American Heart Association, 2009). It is the most important cardiovascular disorder in number of persons affected each year.

Coronary atherosclerosis is the most common cause of CHD and is a chronic disease characterized by stable and unstable periods (Thygesen et al., 2007). Unstable periods manifest themselves in acute coronary syndrome (ACS), the spectrum of clinical syndromes that reflect progression of occlusion in a coronary artery (DeVon, 2008). Unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) are the three disease states categorized under the broader category of ACS. These will be discussed in further detail later in this chapter.

ACS is a major cause of emergency medical care and hospitalization in the United States today. An estimated six million patients with chest pain are evaluated in U.S. emergency departments annually (Atzema, Austin, Tu, & Schull, 2009). One in five of all medical admissions to the hospital is a patient who presents to the emergency department (ED) with chest pain (Body, 2008). Each year, five million ED visits and one and a half million admissions are related to acute coronary syndrome.

The most important goal in the management of ACS is identifying the problem early and initiating prompt intervention. To date, the electrocardiogram (ECG) is the gold standard used for screening, identifying, and evaluating patients with chest pain and anginal equivalents (Kudenchuk et al., 1998). It is the most immediately available diagnostic tool for patients with suspected ACS and is an inexpensive and non-invasive technology for patients with symptoms suggestive of acute myocardial ischemia (Savonitto et al., 1999). The American Heart Association (AHA) and European Society of Cardiology guidelines recommend that all patients who present to the ED with chest pain should have a 12-lead ECG recorded within 10 minutes of arrival (Body, 2008). This recommendation is based on the premise that longer delays are associated with worse outcomes (Anderson et al., 2007; Antman et al., 2004). The presence of acute ischemic changes on the initial ECG, often conducted at presentation to the ED, is associated with a higher risk of cardiac events. Moreover, these acute ischemic changes are unpredictable and dynamic in nature, which suggests that a single snap-shot 12 lead ECG is inadequate and continuous or serial ECG monitoring may be diagnostically superior (Kudenchuk et al., 1998).

Pre-hospital ECG

Conducting a pre-hospital ECG (PH ECG) is becoming the standard of care, especially in the treatment of STEMI (Ting et al., 2008). The AHA gave PH ECG a class I recommendation (supported by strong evidence) in its 2000 Advanced Cardiac Life Support guidelines. The PH ECG is a useful tool for triaging patients to appropriate hospital facilities better equipped to manage ACS; it reduces pre-hospital delay time and enhances the decision to use thrombolytic or other reperfusion therapies appropriately

(Canto et al., 1997). Research findings show that PH ECG is associated with increased usage of reperfusion interventions, shortened time to treatment once a patient reaches the hospital, earlier diagnosis, and greater utilization of cardiac interventions (Alpert, Thygesen, Antman, & Bassand, 2000; Canto et al., 1997; Kudenchuk et al., 1998). Potential long-term benefits of earlier electrocardiography may include: (1) better risk stratification in patients activating '911' with cardiac symptoms, (2) earlier diagnosis of ACS facilitating timelier reperfusion therapy and improved myocardial salvage, (3) better detection of recurrent ischemic events warranting increased surveillance and more aggressive therapies, and (4) improved patient survival and quality of life.

History of PH ECG in Emergency Cardiac Systems of Care

Advanced pre-hospital cardiac care was first widely tested in Belfast in 1966 with the use of Pantridge's mobile coronary care units (Pantridge & Geddes, 1967). Pre-hospital care was initially established in an attempt to prevent deaths occurring from cardiac arrest and to ensure safe transport of victims of myocardial infarction to the hospital. It was also aimed at reducing patient delay in seeking help. Nagel and colleagues (1970) first reported the successful use and benefits of pre-hospital telemetry as part of pre-hospital care in Florida in 1970. Single-lead telemetry with on-line medical control was introduced to the emergency medical system (EMS). Pre-hospital telemetry provided the technologic base for emergency cardiac care and advanced cardiac life support in patients with malignant arrhythmias (Nagel, 1970). However, the single-lead systems did not provide any diagnostic information about ACS. Diagnostic data became available in the mid 1980s when physicians in Western Europe introduced portable 12-lead ECG systems in physician-staffed mobile intensive care units (Aufderheide, 1994;

Ferguson et al., 2003). Today, PH ECG is at the core of decision making in emergency cardiac systems of care. PH ECG provides crucial data that drives early treatment decisions for patients with STEMI (decision to bypass what may be the closest hospital for a further one that offers definitive cardiac care).

Theoretical Framework

The physiological theory of myocardial ischemia guides the practice and research related to PH ECG. Myocardial ischemia occurs when the oxygen supply is insufficient to meet the metabolic demands of myocardial cells in the setting of CHD. Several pathologic mechanisms that decrease myocardial oxygen supply or increase myocardial oxygen demand include atherosclerotic plaque, acute platelet aggregation and thrombosis, vasospasm, failure of microcirculation auto regulation, and poor perfusion pressure (Keeley, Boura, & Grines, 2003). Atherosclerotic plaque is the most common cause of myocardial ischemia. Although the luminal narrowing contributes to clinical manifestations of CHD, it is actually the development of a thrombus at the site of an atherosclerotic plaque that is responsible for ACS (Shah, 2002, 2009). Approximately 75% of thrombi responsible for ACS are precipitated by plaque rupture (Kristensen, Ravn, & Falk, 1997).

Clinical Syndromes of Myocardial Ischemia

Unstable angina is a form of ACS that results from reversible myocardial ischemia. UA occurs when a superficial erosion of a plaque leads to transient episodes of thrombotic vessel occlusion and vasoconstriction at the site of damage. The thrombus is labile and occludes the vessel for 10 to 20 minutes at a time, after which perfusion returns. UA presents as new onset angina, angina occurring at rest, or angina that is increasing in severity or frequency. It is crucial to recognize UA as a warning for impending infarction.

Myocardial infarction manifests itself clinically in subendocardial infarction (NSTEMI) and in transmural infarction (STEMI). The thrombus is less labile and occludes the vessel for prolonged periods of time, leading to cell necrosis and death. If the thrombus lodges permanently in the vessel, then the infarction may extend throughout the myocardium (endocardium to epicardium) resulting in severe cardiac dysfunction (Banasik, 2005).

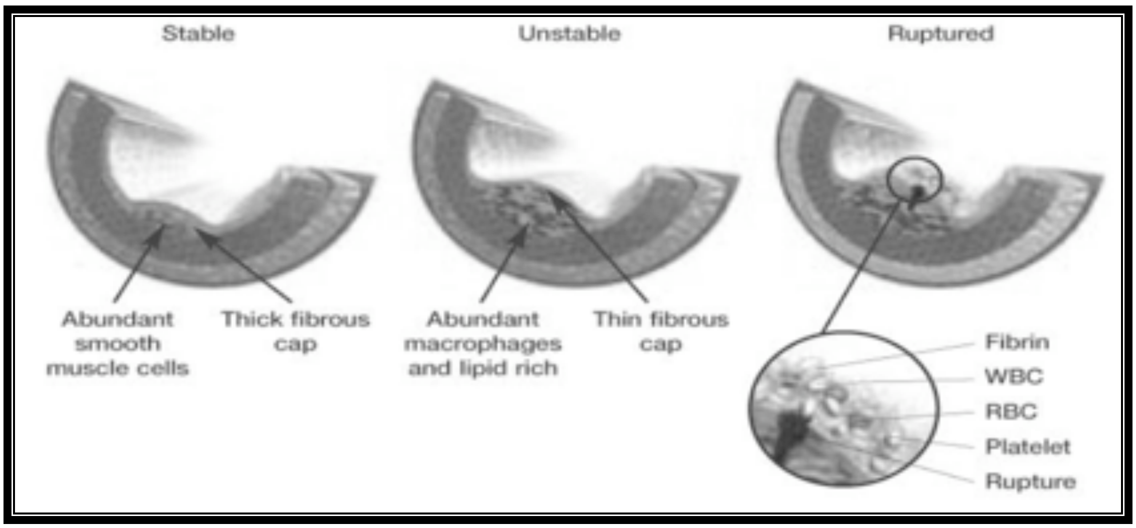

Figure 1. Demonstrates the spectrum of coronary plaque from "stable" to "unstable". The more unstable the plaque, the more likely it is to rupture which subsequently results in a release of prothrombotic and vasoconstrictive factors that result in ACS. Adapted from NCBI/NIH website.

ECG Manifestations of Ischemia

Changes in the intracellular action potential in myocardial ischemia, injury, and infarction frequently result in changes in ECG waveforms, specifically in the ST segment and T wave. A current of injury flows from the uninjured portion towards the injured portion, resulting in ST segment deviation indicative of ischemia. The typical ECG ST segment manifestation of “demand-related” ischemia is ST-segment *depression.* These changes reflect injury to the subendocardium, the innermost layer of the heart. In electrical systole, ischemic cells have a charge of -15 mV and non-ischemic cells have a charge of +5. Thus, the current flows away from the surface electrode, producing ST-segment depression (Drew, 2008).

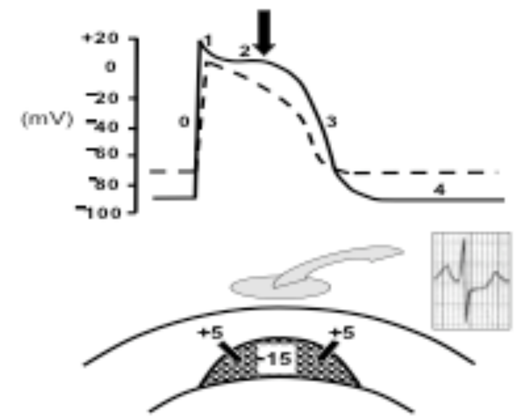

Figure 2. Alteration of action potential in myocardial ischemia that produces ST-segment depression. With permission from B. Drew.

Subepicardial or transmural ischemia injury is manifested in ST-segment *elevation.* ST-segment elevation reflects supply-related ischemia, which is caused by sudden thrombotic occlusion of one of the three major vessels in the heart. Supply-related ischemia impacts the entire thickness of the myocardium, making immediate intervention imperative in order to salvage myocardium. Differences in electrical charges in the action potentials between nonischemic and ischemic cells during systole (phase 0-3) and diastole (phase 4) produce ST-segment elevation (Drew, 2008). ST elevation is actually a combination of T-P lowering and true ST elevation. ECG manifestations of ischemia such as ST elevation caused by supply-related ischemia can help localize the area of ischemic myocardium and identify the culprit artery (Braunwald et al., 2001). Reciprocal changes can be found in ECG leads opposite the ischemic region.

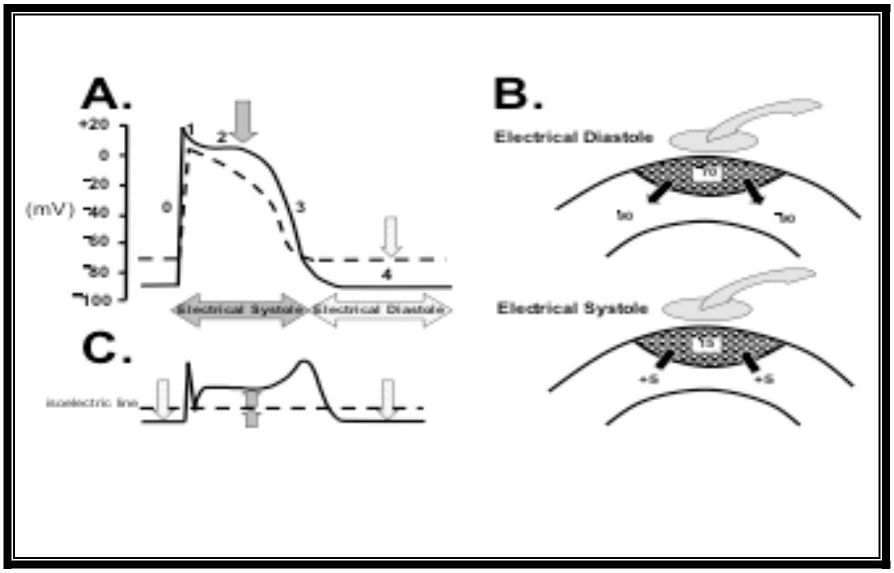

Figure 3. Illustration of alteration of action potential during myocardial ischemia producing ST-segment elevation. With permission from B. Drew.

Methodology

Research Design

This dissertation study is a *secondary* analysis of data obtained from a prospective, randomized controlled trial called *TELE-ELECTROCARDIOGRAPHY IN EMERGENCY CARDIAC CARE (NIH/NINR 5 R01 NR7881).* The research design of the *parent* study will be described below, and specific details of the *secondary* analysis will be described in Chapters three and four.

The *parent* study utilized a randomized controlled design with two study groups. The main aim of the *parent* study was to determine whether pre-hospital ST-segment monitoring with automatic telephone transmission of ECGs to the target hospital improved hospital time to treatment for ACS and improved patient outcome over the span of the 5-year study. Subjects were randomized to study group by a dedicated desktop computer located at one of the target emergency departments. The experimental group received the intervention which included synthesized 12-lead ECG monitoring with specialized ischemia monitoring software (Lifepak12, Physio-Control, Redmond, Washington) and automatic printout of ST event ECGs in the target ED. The control group received routine pre-hospital emergency cardiac care which included cardiac monitoring of a single ECG lead for detection of cardiac arrhythmias and a 12-lead snapshot ECG after ED arrival. PH ECG data were stored in a software program (CodeStat Suite version 8.0, Physio-Control, Redmond, Washington) that was utilized for offline analysis.

The *parent* study began in June 2003 and ended on June 31, 2008 and enrolled a total of 794 subjects (all STEMI, NSTEMI, UA, and non-ACS diagnoses). Of these, 40 subjects were enrolled more than once. Follow-up was conducted at multiple time points (30-day, 1-year, 2-year, 3-year, and 4-years). Hospitalization and mortality outcome data were collected at each of these follow-up time periods.

Research Setting

The study took place in Santa Cruz County, which has both urban and rural areas. The county is ethnically diverse with a population of Spanish-speaking only Hispanics and migrant farm workers who are economically disadvantaged. There are two hospitals in the county and a total of 22 emergency vehicles serving the entire county. All emergency vehicles were equipped with study devices. EMS personnel consisted of firemen who were credentialed as emergency medical technicians and paramedics.

Sample

The sample included all consenting patients in Santa Cruz County ≥ 30 years old who called "911" and EMS personnel judged to have possible acute ischemia/infarction and were routinely placed on a cardiac monitor. The sample included individuals with complaints of non-traumatic chest pain or anginal equivalent symptoms (arm, shoulder, or jaw pain, or shortness of breath). Exclusion criteria included participants who were unwilling or unable to consent. This *secondary* analysis utilized all subjects who were enrolled in the *parent* study who had a PH ECG available for interpretation.

The Institutional Review Board (IRB) approved the following two-step consent procedure for the *parent* study. The initial consent occurred in the pre-hospital setting by community consent. Consent was not obtained in the field since (1) noninvasive ECG monitoring posed no risk of physical harm, (2) noninvasive ECG monitoring is considered the standard of care for pre-hospital emergency cardiac care and is routinely performed by EMS personnel without patient consent, and, (3) written consent could have caused scene delays which could be harmful to the patient. Once the patient was comfortable and hemodynamically stable, research nurses in the hospital obtained written consent to obtain permission to use: (1) the already collected PH ECG data for research purposes, (2) medical record information and, (3) permission to contact the patient by telephone for follow-up. The written consent was documented on the data collection form and all data were stored in a locked file cabinet in the principle investigator's research lab. If patients did not consent to be in the study, their PH ECG data was not used. Eighty-one patients refused participation in the study.

Data Collection Methods

The procedures of the *parent* study are summarized below:

1. EMS personnel applied study monitors to all patients calling "911" for chest pain and/or anginal equivalents.

2. Subjects were taken to one of two target emergency departments.

3. A trained research nurse approached subjects and written informed consent was obtained.

4. Research nurses collected data (descriptive data and clinical outcomes) from subject and medical records.

5. Data were collected on study forms that were entered into a password protected database (Microsoft Access, Redmond, Washington). The database was managed remotely in San Francisco and backed up daily.

6. Follow-up telephone calls were placed to subjects at: 30 days, 1-year, 2-year, 3-year, and 4-year by research nurses. Data were entered into the database.

Instruments

ECG transmission device

The ST SMART device replaced the cumbersome 10-electrode standard 12-lead ECG with a simple 5-electrode configuration that provided both a 12-lead ECG and cardiac monitoring. A validation study to determine the diagnostic agreement between the two ECG methods was conducted prior to the *parent* study (Drew et al., 2004). There was a high percentage of agreement between synthesized and standard ECGs for diagnoses of interest for pre-hospital care. The ST SMART device utilized ischemia monitoring software designed for exercise stress testing that had powerful noise reduction technology to ensure high quality ECGs. ECGs were automatically transmitted by cell phone to the target ED. To ensure successful ECG transmissions, the device automatically redialed if the EMS vehicle was in a location where cellular telephone communication was unavailable.

Computer-assistance

The ST SMART computer had specialized ST segment monitoring software that continuously analyzed all 12 ECG leads and triggered an ECG print-out in the ED for any ST change greater than 200 μV (changes of acute ischemia) in one lead that lasted for at least one minute. Because ST segment changes of ischemia are often subtle, it is often impossible for humans to detect such changes by "eye-balling" waveforms on a cardiac monitor. The difficulty in identifying subtle ischemia changes is especially true for EMS personnel who are busy with other emergency cardiac care tasks. Computerized ECG measurements eliminate human bias and can precisely measure waveforms to a resolution of 10 μV, significantly more so than the human eye is able to detect at 50 μV or greater. Moreover, routinely used portable monitor-defibrillators used by EMS personnel display just one ECG lead that is unlikely to be the lead showing maximal ST segment deviation.

Procedures

Measurements for this *secondary* analysis study include: demographics, outcomes (in-hospital and long-term), and ECG changes of ischemia. Demographic information was obtained in the *parent* study via medical record review.
Outcome measures were collected by follow-up telephone calls, medical chart review, and by the Social Security Death Registry website. For this study, specific in-hospital complications related to ACS were analyzed. Those reported in the literature include

recurrent angina with and without ECG changes, heart failure, arrhythmia disturbances, and death (Antman et al., 2004). Further details about the measurements analyzed for this dissertation will be discussed in Chapters three and four.

ECG data were collected and stored electronically in CodeStat Suite (CodeStat Suite version 8.0, Physio-Control, Redmond, Washington), a software program that managed the pre-hospital data. ECGs obtained in the pre-hospital setting were printed out and were analyzed (ST-T wave changes, Q-wave, LVH, BBB, and arrhythmia). When one or more PH ECG was acquired (by automated detection of ischemic changes), all were analyzed applying the new universal criteria for the diagnosis of ACS. These criteria were recently published to increase the sensitivity and specificity of the standard 12-lead ECG. The new criteria for ECG manifestations of ischemia consider gender differences and are listed below (Thygesen et al., 2007).

Criteria for ECG manifestations of acute myocardial ischemia (in the absence of LVH and LBBB) include:

(1) ST elevation at the J-point in two contiguous leads with the cut-off points: ≥ 0.2mV in men or ≥ 0.15mV in women in leads V2-V3 and/or ≥ 0.1mV in other leads;

(2) ST-depression and T-wave changes redefined by new horizontal or down-sloping ST depression ≥ 0.05mV in two contiguous leads and /or T inversion ≥ 0.1mV in two contiguous leads with prominent R-wave or R/S ratio >1.

Criteria for ECG changes associated with prior myocardial infarction include:

Leads V_2 -V_3: Any Q-wave in leads $\geq$0.02s or QS complex;

Leads I, II, aVL, aVF, or V_4-V_6: Q-wave $\geq$0.03s and $\geq$0.1 mV deep or QS complex in any two contiguous leads;

Leads V_1-V_2: R-wave $\geq$0.04s and R/S $\geq$1 with a concordant positive T-wave in the absence of a conduction defect.

Dissertation Aims

The goal of this dissertation study is to provide more comprehensive information about the diagnostic accuracy (sensitivity and specificity) and prognostic value of PH ECG triggered by ST-segment monitoring. This dissertation is organized into five chapters.

Chapter one provides an introduction to the dissertation and presents a background, history, theoretical framework, and an overview that includes the research design of the *parent* study.

Chapter two is a critical literature review related to PH ECG. Important gaps in current knowledge are identified.

Chapter three is a research manuscript that presents the findings of a study that determined the sensitivity and specificity of PH ECG and assessed the diagnostic performance of PH ECG when used in conjunction with the initial 12-lead hospital ECG. The research findings highlight the importance of serial ECG data to enhance the diagnosis of ACS.

Chapter four is a research manuscript that presents the findings of a study that examined the prognostic value of ischemia identified on the PH ECG and its impact on adverse hospital outcomes.

Chapter five is a conclusion of the research findings of this dissertation. Future directions are discussed.

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Chapter 2

Critical Literature Review of Pre-hospital Electrocardiography

Abstract

Introduction: The American Heart Association and other scientific guidelines recommend emergency medical services (EMS) acquire pre-hospital electrocardiography (PH ECG) on all patients with symptoms of acute coronary syndrome (ACS). The purpose of this article is to critically review the scientific literature about pre-hospital electrocardiography and identify gaps in knowledge.

Methods: Using multiple search terms, PubMed and Web of Science databases were searched for relevant information.

Results: PH ECG has been associated with reduced pre-hospital delay time, increased use of reperfusion interventions, earlier diagnosis, and faster time to treatment.

Discussion: PH ECG plays a major role in emergency cardiac systems of care and can facilitate early intervention by identifying patients with ACS sooner. More research is needed to better understand the diagnostic accuracy and prognostic implications of PH ECG.

Introduction and Significance

To date, much of the focus of pre-hospital electrocardiography (PH ECG) has been on its role in pre-hospital cardiac systems of care for patients with ST elevation myocardial infarction (STEMI). [1] Numerous studies have shown that reporting or transmitting a PH ECG to the emergency department (ED) is an integral part of cardiac systems of care. [2-5] PH ECG drives the decision to bypass what may be the closest hospital for a further one that offers definitive care (percutaneous coronary intervention) for patients with STEMI. PH ECG facilitates earlier diagnosis and is an essential component of any rapid intervention strategy. [5] The main benefit of PH ECG lies in its potential to reduce the overall time to administration of reperfusion therapy through several mechanisms. [6,7] The AHA gave pre-hospital ECG a class I recommendation (supported by strong evidence) in its 2000 Advanced Cardiac Life Support guidelines, and is pushing hospital systems to integrate PH ECG into care for patients with acute coronary syndrome (ACS). [1]

Search Strategies

A review of the literature was conducted using PubMed and Web of Science databases to identify key articles about PH ECG literature. Search terms used alone, and in combination with "AND" and "OR" included: *pre-hospital ECG, electrocardiography, emergency medical services, acute coronary syndrome, myocardial ischemia,* and *myocardial infarction.* Search limitations were utilized: human, research (clinical trials, experimental), core journals, and adult with relevant journals selected for inclusion. Articles have been conceptualized and organized into several themes that include: clinical effects of PH ECG (timing, roles, effects on patient outcome and characteristics of patients with PH ECG), diagnostic performance, and prognostic/predictive value of early ECG. A summary of the 18 research articles selected for this review is presented in Table 1. A list of common abbreviations used in the summary table is presented in Table 2.

Review of Literature

Measures of Clinical Effect

Effects of PH ECG on Time, Reperfusion Rate, and Other Clinical Factors

Most of the literature about PH ECG has focused on the clinical effects of PH ECG on time savings and patient outcomes. Both prospective nonrandomized studies and randomized trials have analyzed time intervals, early ventricular function, mortality, and long-term survival as measures of clinical effect.[8] The primary time intervals that have been the reported in the literature include, but are not limited to: symptom onset until first ECG, time to hospital arrival, and time to reperfusion intervention. To date, the principle clinical benefit of the pre-hospital ECG is in the reduction of time from cardiac symptom onset to initiation of reperfusion therapy.[6,7,9] PH ECG has been associated with increased usage of reperfusion interventions, shortened time to treatments once a patient reaches the hospital, and a greater utilization of cardiac interventions.[9]

Canto and colleagues conducted the first large study that compared patients with a PH ECG (N=3,768) with patients without a PH ECG (N=66,995) who were enrolled in the National Registry of Myocardial Infarction (NRMI-2) database.[9] This was the first study to evaluate the clinical effects of PH ECG. The investigators found that both the median times from symptom onset to first ECG acquisition (120 vs. 108 min) and to hospital arrival (152 vs. 91 min) were significantly longer ($p<0.001$) in the PH ECG group than in the no PH ECG group. Despite longer times, however, the hospital time to reperfusion therapy was significantly shorter in the PH ECG group than in the no PH ECG group (thrombolytic therapy ["door to drug"]: 30 vs. 40 min and percutaneous coronary intervention ["door to balloon"]: 92 vs. 115 min, $p<0.001$). Furthermore, the proportion of patients who received reperfusion therapy was significantly greater in the PH ECG versus the no PH ECG group (thrombolytic therapy: 43% vs. 37% and percutaneous coronary intervention: 11% vs. 7%, $p<0.001$). Canto and colleagues found no significant differences in outcomes of recurrent ischemia or recurrent infarction between the two groups.[9] However, the PH ECG group experienced less heart failure and hypotension and the unadjusted hospital mortality for the PH ECG group was significantly lower than in the no PH ECG group (8% vs. 12%, $p<0.001$). Lastly, they found that PH ECG was an independent predictor of lower overall mortality.[9]

Canto's study was innovative since the investigators further identified and described specific characteristics about hospitals in communities with PH ECG capability. They found such facilities tended to have a larger mean number of staffed beds and ED visits per year than those facilities without PH ECG capability.[9] PH ECG community facilities were also more likely to have coronary arteriography, angioplasty, and cardiac surgery capabilities than hospitals not receiving patients with PH ECG. Of note, more than 75% of patients in this study presented to hospitals in communities with PH ECG capabilities, although PH ECG was only obtained in a minority of patients.[9]

Although a seminal study on the topic of PH ECG, a major limitation of this study was the inability to distinguish between PH ECGs obtained by EMS versus ECGs obtained in a physician's office. The American Heart Association recommends that patients call 911 (and not their physician) if they experience symptoms of acute myocardial infarction. If Canto et al.[9] had reported on the time from symptom onset to first ECG in the subgroup who appropriately activated the EMS system, there might have been a shorter median time to first ECG in the PH ECG group compared with the no PH ECG group. Study findings may be limited since they are based on hospitals in the NRMI database. There is potential for nonconsecutive patient enrollment, lack of independent on-site validation of data forms and the fact that registry hospitals may not be representative of all U.S. hospitals.

Brainard et al.[6] conducted a systematic review of research literature that reported time savings of pre-hospital 12-lead ECG. This meta-analysis of studies conducted in the United States (1966-2004) was necessary because the American Heart Association's Class I recommendation for a PH ECG was based entirely upon studies conducted in Europe. Thus it was unclear whether the European study findings could be applied to the American emergency cardiac systems of care. For example, much of the European data were collected in EMS systems that had ambulances staffed with physicians or paramedics who administered fibrinolytics in the field, characteristics not typical of the U.S. One of the major strengths of this meta-analysis was its inclusion of studies that had strong study designs (including treatment and control groups) and appropriate outcome measures. There were several factors that enhanced the internal validity of the meta-analysis. Studies in which patients received PH ECGs acquired by EMS were included, unlike that of the Canto study [9] that also included ECGs obtained in a physician's office. Extraneous variance was controlled for since all studies included patients admitted to the emergency department, not directly to the cardiac catheterization laboratory or coronary care units. Time savings findings for this meta-analysis were concluded from four different articles (N=99) and were consistent with the Canto study [9] findings. There was an average reduction of 22 minutes (95% CI, 20.04-24.0) in time to hospital reperfusion intervention between those who received PH ECG and those who did not. The mean time to reperfusion was 36.5 minutes (95% CI, 32.4-40.6) for the PH ECG group versus 58.5 minutes (95% CI, 56.1-60.9) for the no PH ECG group.

It is unclear whether reperfusion intervention included fibrinolytic therapy, percutaneous coronary intervention (PCI), or both which may be a threat to construct validity. Other inherent limitations of this meta-analysis are its dependency on previously published research and the accompanying bias of each. Lastly, the studies that were included spanned nearly a 40-year time period and it is likely that time to treatment improvements may have been due to many factors in addition to whether PH ECGs were performed.

Curtis and colleagues [7] conducted a large observational study of data from the National Registry of Myocardial Infarction (NRMI-4) database to determine the effects of PH ECG on door-to-reperfusion times.[7] This more recent study can be directly compared with the Canto study [9] in its design and purpose. The study included 56,647 patients with acute myocardial infarction enrolled in NRMI-4 between January 2000 and December 2002. Inclusion criteria were restricted to patients with STEMI or left bundle branch block identified on their first ECG who received reperfusion therapy (within 6 hours of admission). The primary outcome of interest was time from hospital arrival to either 1) administration of fibrinolytic therapy (door-to-drug) or 2) time to first PCI balloon inflation (door-to-balloon). The acquisition of PH ECG was associated with significantly shorter door to reperfusion intervention times. The mean door-to-drug time was 24.6 minutes for patients with PH ECG and 34.5 minutes for patients without PH ECG ($p<0.001$). The mean door-to-balloon time was 83.9 minutes for patients with PH ECG and 107.7 minutes for those without PH ECG ($p<0.001$). These findings are in accordance with the previous studies that have been evaluated and may demonstrate the stability of PH ECG benefits over time. An important difference from the Canto study [9] is the interval between symptom onset and hospital arrival time.[7] There was no increase in time in this study, in contrast to the longer symptom to hospital arrival interval that Canto and colleagues [9] reported in 1997. In fact, the mean time was shorter for both the fibrinolytic and PCI cohorts receiving PH ECG (83 versus 95 minutes, $p<0.001$; 80 versus 103 minutes, $p<0.001$).[7] This shorter time may be explained by paramedics responding more quickly to patients they perceived as having acute myocardial infarction. Unlike previous studies reported, Curtis et al. added the important consideration of guideline recommendations in their findings. In the fibrinolytic cohort, 60.6% (95% CI, 58.1-63.0) of patients with PH ECG received therapy within the guideline recommended 30 minutes of hospital arrival as compared to 40.8% (95% CI, 40.3-41.3) of those without PH ECG ($p<0.001$). In the PCI cohort, 55.2% (95% CI, 52.9-57.6) of patients with PH ECG received reperfusion therapy within 90 minutes as compared to 33.1% (95% CI, 32.5-33.8) of those without PH ECG ($p<0.001$).

Eckstein and colleagues [10] conducted a retrospective study that compared door-to-balloon times for STEMI patients transported by paramedics who received a PH ECG with patients who arrived via self-transport. This is an important comparison because a majority of patients with ACS present to emergency departments by self-transport.[11] Four urban hospitals with PCI capability were included in the study. A total of 234 patients were evaluated between January 2005 and December 2005. Inclusion criteria were explicitly stated and were an admission diagnosis of STEMI and a hospital discharge diagnosis of acute myocardial infarction. The time variables that were evaluated were 1) time-to-catheterization laboratory and 2) time-to-balloon inflation. Medical records were reviewed for data collection.

In agreement with the previous studies discussed, clinical time intervals were less for patients who received PH ECG. The median times from ED arrival to arrival to the catheterization laboratory were 64 minutes for the EMS transport group versus 77 minutes for the self-transport group (95% CI of the time savings, 18.5-27.2, $p<0.05$). Median door-to-balloon times were 95 minutes for the EMS transport group versus 108 minutes in the self-transport group (95% CI of the time savings, 3.5-16.4, $p<0.05$). The time savings of 13 minutes in door-to-balloon time was less than the 22 minutes reported in the meta-analysis by Brainard et al. [6] in 2005. EMS transport was associated with shorter door-to-balloon times and while this did not achieve statistical significance, this may be a clinically significant finding. Some of the limitations of this study were inherent due to its retrospective design since data were abstracted from medical records, which may be a threat to the internal validity of the study because of inaccurate or missing documentation. This study was conducted in an urban setting that was establishing STEMI receiving centers; so its findings may not be generalizable to suburban/rural hospitals.

Diercks and colleagues [12] recently conducted a very large study to determine the association of PH ECG and the timing of reperfusion therapy for STEMI patients. These investigators also wanted to determine nationwide usage and impact of PH ECGs.[12] Subjects were enrolled in the National Cardiovascular Data Registry (NCDR ACTION) between January-December 2007. A large cohort of 12,097 patients was enrolled who presented with STEMI by EMS or self-transport and met the following inclusion criteria: 1) persistent ST-segment elevation or new left bundle branch block, 2) presenting within 24 hours of ischemic symptom onset, 3) initial evaluation in the emergency department and, 4) non-transfer patients. Among 7,098 patients transported by EMS, only 1,941 (24.7%) received a pre-hospital ECG. Patients with PH ECG were more likely to undergo primary PCI and less likely to receive no reperfusion therapy compared with those who did not receive PH ECG. Additionally, those with PH ECG achieved faster door-to-drug (19 min versus 29 min, $p<0.003$) and door-to-balloon times (61 min versus 75 min, $p<0.001$) than those without PH ECG.[12] Diercks and colleagues found those with PH ECG were more likely to meet time to treatment guideline recommendations for both fibrinolytic therapy (49.1 versus 72.4, $p=0.05$) and PCI (70.0 versus 82.3, $p<0.001$), confirming findings by the study conducted by Curtis [7] and colleagues in 2006.

Most recently, Drew and colleagues conducted a large randomized clinical trial that compared patients with and without PH ECG in paramedic scene time (time spent in field with no wheels rolling) and time-to-treatment (STEMI, door-to-balloon; non-STEMI and unstable angina pectoris, door-to-first intravenous ACS drug).[13] A total of 794 patients were enrolled from June 2003-June 2008. Inclusion criteria included all patients transported by ambulance for symptoms suggestive of ACS, ≥ 30 years of age, were not in cardiac arrest at EMS arrival, had a successful PH ECG transmission, and consented to participate in the study. [13] A total of 74% of patients who called 911 with

ACS symptoms over the 5-year study period received PH ECG. The proportion of patients with a final ACS diagnosis (STEMI, NSTEMI, UA) who had PH ECG transmitted was 57%. This is higher than the 24.7% previously reported by Diercks et al.[12], which differed since only patients with STEMI were included in that study. Mean scene time for those with PH ECG was two minutes longer than those without (18 $\pm$ 6 minutes compared to 16 $\pm$ 6 minutes, $p<0.05$). Mean door-to-balloon time in STEMI patients with PH ECG was 78 $\pm$ 22 minutes compared to 101 $\pm$ 56 minutes in those without PH ECG ($p = 0.197$). Mean door-to-first intravenous drug in NSTEMI and UA patients was 23 $\pm$ 12 minutes in those with PH ECG versus 31 $\pm$ 16 minutes in those without ($p<0.05$).

This study was the first to prospectively evaluate time to reperfusion and outcomes in patients randomized to PH ECG versus no PH ECG. While the faster time-to-intervention findings are in agreement with previously discussed studies about STEMI [6,7,9,12], this study further examined times for non-STEMI and unstable angina. It was also the first to utilize a 5-electrode lead configuration with continuous ST-segment monitoring in the field from which a synthesized PH ECG was obtained. This simple strategy was associated with significantly greater paramedic PH ECG acquisition.[13]

Effects of PH ECG on Mortality, Ejection Fraction, Reinfarction, and Stroke

Two studies have evaluated the clinical effect of PH ECG on mortality and other patient outcomes. Ioanndis and colleagues conducted a meta-analysis to determine characteristics of the clinical effects of PH ECG.[8] A total of 10 studies, both prospective and retrospective, were reviewed. Inclusion criteria were explicit and included patients in the pre-hospital setting with chest pain who received an ECG. In a review of two nonrandomized studies, left ventricular ejection fraction (at discharge or within one week after admission) was better in the PH ECG groups and reached statistical significance. Conversely, short-term effects on ejection fraction from five randomized trials showed no significant difference between PH ECG and the control groups. Finally, in-hospital mortality was 8% in the PH ECG group versus 12% in the control group ($p<0.001$). Cumulative findings in these four randomized trials suggested an overall survival benefit to PH ECG groups. The impact on longer-term mortality (1 and 2 year follow-up) was inconclusive, since only four trials attempted to evaluate long-term mortality and all four had missing data. This is a problem inherent to longitudinal study designs. While statistical findings were reported for some of the characteristics discussed above, the study was weakened by a lack of statistical reporting for several important characteristics that were evaluated. This makes it difficult to draw conclusions about PH ECG from the meta-analysis.

Zeymer and colleagues [14] published a recent study to evaluate the in-hospital fate of patients with STEMI diagnosed by PH ECG. This German study enrolled consecutive patients who contacted EMS for chest pain or anginal equivalent from 20 minutes to 24 hours of symptom onset and demonstrated ST-segment elevation suggestive of STEMI on PH ECG.[13] A total of 2,326 subjects were enrolled between March 2003 and December 2004. The accompanying physician diagnosed STEMI in the field in the ambulance, a difference between the German and U.S. EMS systems. Although the median time intervals between PH ECG and reperfusion therapy were short (PH ECG-to-pre-hospital fibrinolysis 10 minutes; inhospital fibrinolysis 52 minutes; primary PCI 86 minutes), they observed no significant differences in mortality, the rate of reinfarction, stroke, and major bleeding complications between patients treated with pre-hospital fibrinolysis or primary PCI.

Summary

Research findings consistently show that PH ECG is associated with both significantly shorter door-to-reperfusion times for both fibrinolytic therapy and PCI. Furthermore, a higher proportion of patients with PH ECG receive reperfusion therapy within guideline-recommended timeframes. The discrepancies in scene time or symptom onset to hospital arrival time in the literature may be due to variability in data reporting. It is difficult for patients to reliably recall when their symptoms began. Other studies may have obtained these data from EMS reports. More importantly, longer scene times do not appear to impact a faster time to reperfusion therapy in patients who receive PH ECG. Lastly, the in-hospital survival benefit of PH ECG is inconclusive and to date, no studies have evaluated the implications on long-term survival for those who receive PH ECG.

Studies Evaluating the Diagnostic Performance of PH ECG

Sensitivity and specificity

Two articles have focused on the diagnostic accuracy and performance of PH ECG. In 1998, Kudenchuk and colleagues [5] conducted a large study to characterize the frequency and serial evolution of early ECG changes in patients with and without myocardial ischemia and infarction. This was a secondary analysis of a large randomized clinical trial that compared pre-hospital and in-hospital thrombolysis. The investigators wanted to determine if ECG screening before hospital admission improved the diagnosis of ACS in patients with chest pain of suspected cardiac origin in their secondary analysis.

Although this is an older study, it is innovative in their added consideration of serial ECG findings, since they compared the pre-hospital and initial hospital ECG in 3027 consecutive patients. Of note, 362 of these patients were randomized to pre-hospital versus hospital thrombolysis and 2,665 did not participate in the RCT. Two different experienced electrocardiographers who were blinded analyzed each of the ECGs. This enhanced the study design since a blinded approach minimized bias. ST-segment elevation was defined as ≥0.1 millivolt (≥1 mm) in at least two contiguous leads. ST-segment depression was defined as ≥1 mm horizontal or downsloping ST-segment depression in two or more contiguous leads. Each was diagnostic in the absence of left bundle branch block (LBBB), ventricular pacing, or an idioventricular rhythm, all known confounders of the ST segment. Pathologic Q waves were defined as an initial negative QRS deflection ≥40 milliseconds in duration in at least two contiguous ECG leads.[5]

Investigators found that ST-segment changes, specifically ST elevation, ST depression, or T-wave inversion, were more common in subjects with ACS than in subjects without ACS ($p<0.00001$). Q-waves were more prevalent on the initial hospital ECG than on the PH ECG in patients with acute ischemia or infarction (31% vs. 21%, $p<0.00001$). The investigators found no significant differences in the prevalence of ST-segment elevation, ST-segment depression, T-wave inversion, or left bundle branch block between PH ECG and initial hospital ECG. Although time in between the PH ECG and hospital ECG was not reported, one could speculate the ECG may not evolve much in fast transit times. The identification of any abnormality in ST segment, T or Q wave or LBBB on either PH ECG or initial hospital ECG had identical sensitivity (80%), specificity (60%), and positive predictive value (64%) for detecting acute myocardial ischemia or infarction (p<0.00001). The reported sensitivity is unusually high as most literature reports the ECG to have 50% sensitivity for AMI. The sensitivity may be inflated since it included *any* sign of ischemic abnormalities, not just that for acute myocardial infarction.

With respect to serial ECG comparisons, the investigators reported the prevalence of ST-segment elevation on the PH ECG to be higher than on the hospital ECG obtained 20-30 minutes later (p=0.03).[5] To avoid confounding effects of thrombolysis on the ECG, serial changes were evaluated only in the 2,665 patients who were not part of the RCT. Moreover, the serial ECG changes between the PH and initial hospital ECG proved important because the ST-segment changes often evolved to diagnostic proportions in patients with acute ischemia or infarction between the two ECG tracings (p<0.0000001). The dynamic evolution of changes between PH ECG and hospital ECG was a critical discriminator between patients with and without ACS. It improved the diagnostic sensitivity of *ST elevation alone* for myocardial ischemia or infarction from 34% to 46%, with a reduction in specificity from 96% to 93% and a positive predictive value from 88% to 84% (all p<0.00004). There were evolving changes between PH ECG and hospital ECG of *ST-segment elevation, depression, T wave inversion, developing Q waves, or LBBB* in 57% of patients with ACS as compared with 32% of patients without ACS (p=0.0000001). Overall, the serial evolution of these changes between the PH ECG and initial hospital ECG improved the diagnostic sensitivity of the ECG for ACS from 80% to 87% with a decline in specificity (60% to 50%) and positive predictive value (64% to 60%)(p<0.000006). So, by themselves, ST segment changes that were mutually exclusive on PH ECG or initial hospital ECG were less sensitive but more specific for acute ischemia or infarction. However, serial ST segment changes between PH ECG and initial hospital ECG significantly improved the sensitivity for diagnosing ACS with a decreased specificity and positive predictive value.[5]

In addition to clinical characteristics, Ioannidis and colleagues [8] also determined the diagnostic performance of PH ECG and evaluated sensitivity, specificity, and diagnostic odds ratio in their meta-analysis. Five of the studies that were included focused on patients with myocardial ischemia while eight studies evaluated patients with myocardial infarction. The investigators reported individual findings for both subgroups: myocardial ischemia and myocardial infarction. Overall, the diagnostic accuracy for myocardial ischemia had 76% sensitivity, 88% specificity, and a diagnostic odds ratio of 23. The sensitivity for myocardial infarction was 68%, specificity 97%, and a diagnostic odds ratio of 104. Because these findings were based on multiple studies, differences in the stringency of how ECG abnormalities were defined may have impacted the results. Furthermore, multiple interpreters of ECG data could have further influenced results. The authors appropriately acknowledged these potential threats in their meta-analysis discussion.

Summary

The PH ECG has diagnostic accuracy for myocardial infarction and myocardial ischemia similar to that of the initial hospital ECG. Serial ECG recordings may enhance the diagnostic sensitivity for an acute coronary event as compared to abnormalities on a single tracing. Serial changes offer the opportunity to observe changes between tracings that may be more difficult to interpret individually. Both studies by Kundenchak [5] and Ioannidis [8] reported higher than usual sensitivities. Study limitations may include different expertise in ECG interpretation, differences in the stringency of ECG abnormality definitions, and differences in the definition of coronary ischemia.

Prognostic Value of Pre-hospital and Early Electrocardiography

Studies Evaluating Prognostic Value of ECG in the Pre-hospital Setting

Although an older study, Grijseels and colleagues [15] conducted the first prospective study in 1995 (Rotterdam Pre-hospital ECG Project) to better distinguish patients with a low probability for acute cardiac pathology (i.e. stable angina, atypical chest pain, heart failure) from those with a high probability (i.e. unstable angina, myocardial infarction) using PH ECG and presenting symptoms. They evaluated the accuracy of predictive algorithms in the pre-hospital setting that were created to distinguish patients with ACS from those with less acute or non-cardiac diagnoses.[15] A total of 1005 patients with symptoms of cardiac ischemia were enrolled, making this a large sample. All were initially evaluated by a general practitioner and subsequently transferred to the hospital by ambulance. An ambulance nurse performed a pre-hospital 12-lead ECG prior to being transferred to the hospital. The presence of an abnormal ECG proved to be the most important predictor of an ACS diagnosis (OR 4.2; CI 95%). Abnormal ECG criteria included ventricular rhythm, pacemaker rhythm, Q-wave with duration $\geq$ 30 ms, right or left bundle branch block, left ventricular hypertrophy, ST elevation $\geq$ 0.05 mV, ST depression >0.025 mV, or T wave abnormality of -0.1 mV in $\geq$ 2 leads.[15] Other independent predictors of acute cardiac pathology included male gender, radiation of chest pain to the neck and left arm, nausea/diaphoresis, and prior cardiovascular disease, all which have been reported in previous literature. While the findings were important and intriguing, the sample did not fully represent all patients who contact EMS with complaints of ACS since these were referred from general practitioners' offices. ECG findings were collapsed into three categories 1) normal or non-specific ECG, 2) abnormal ECG; and 3) extensive myocardial infarction. Publishing the specific ECG findings that impacted the prognostic value for ACS in the pre-hospital setting may have strengthened the study and provided more stringent criteria for risk assessment of this vulnerable population.

Svensson and colleagues [16] sought to evaluate factors that identify patients with ACS prior to hospital admission in a more recent prospective observational study. Different than the previous study by Grijseels [15], they utilized a consecutive sample of all patients activating EMS for acute chest pain or other symptoms concerning for cardiac ischemia in the cities of Stockholm and Gothenburg. There were a total of 538 cases involved, of which 511 were independent (i.e., not repeat) patients. In patients *with and without ST elevation*, ST-segment depression in the PH ECG tracing was found to have the highest independent predictive value for a combined end point ACS/AMI diagnosis (OR 5.04, 2.75-9.22, $p<0.05$), followed by T-wave inversion (OR 2.62, 1.23-5.58, $p<0.05$). Among patients with ST-segment depression, 38% developed an acute myocardial infarction and those with Q-waves had an increased incidence of ACS/AMI diagnosis.[16] These findings were not statistically significant but may have important clinical implications. In patients *without ST elevation*, the likelihood of an acute coronary syndrome/myocardial infarction was higher among patients with ST depression ($p<0.0001$) and T-wave inversion ($p<0.005$) than patients with Q-waves. These findings are consistent with other studies that indicate ST depression on a 12-lead standard ECG is associated with an adverse prognosis.[16] In patients *with ST elevation*, the only factor associated with an increased likelihood of AMI was the presence of ST depression in other leads (OR 3.94, 1.26-12.38, $p<0.05$).

Both of the studies [15,16] reported were conducted in Europe where there are different systems of care, thus their generalizability to other systems may be limited. For example, ambulances were equipped with nurses who conducted the pre-hospital ECG. It is likely their training is different than that of paramedics' in the United States.

Herlitz and colleagues [17] did not utilize PH ECG; however, their study is relevant because it was the first to evaluate the ability of the initial hospital ECG to predict a life-threatening disease or death (30 day and 1 year mortality) among ambulance patients transported for chest pain and/or anginal equivalent symptoms. The definition of life threatening disease included, but was not limited to: acute myocardial infarction, unstable angina, pulmonary edema, acute renal failure, aortic aneurysm, stroke, cardiac arrest, and ventricular tachycardia. ECG findings on admission to the emergency department were analyzed. The investigators found that all ECG signs of ischemia predicted the occurrence of a life threatening disease; whereas only ST elevation and ST depression predicted death. They also reported that patients with a non-sinus rhythm finding on their admission ECG were 1.97 times more likely to die within one year. Some limitations to this study were its retrospective design because data were collected from ambulance run forms, which inherently may have human errors due to paramedics working under pressure and being in a hurry. The lack of standardization in data collection could potentially impact the validity and reliability of this study. The study lacked discussion of who determined ECG signs of ischemia nor were there explicit criteria about how these specific signs were operationally defined.

Studies Evaluating Prognostic Value of Initial ECG in the Hospital Setting

Several studies have established the initial hospital ECG performed in the ED as a prognostic indicator for ACS patients. Early ECG allows for immediate risk stratification across the spectrum of ACS. Savonitto and colleagues [18] conducted a large study (N=12,124) to specifically determine the prognostic value of various ECG presentations of acute myocardial ischemia. The main dependent variable was the ability of the initial ECG to predict death or myocardial reinfarction during the first 30 days of follow-up. [18] The study design was a retrospective analysis of the initial ECGs of patients enrolled in the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Inclusion criteria for this important trial were patients who presented to the ED with chest pain that started within 12 hours and had ischemic changes on their initial ECG. Specific ECG criteria included the presence of either transient or persistent ST-segment elevation or depression of more than 0.05 mV, or persistent and definite T-wave inversion of more than 0.1 mV. Four groups characterized findings: isolated T-wave inversion, ST-segment elevation, ST-segment depression, and ST-segment elevation and depression. Those with ST-segment depression had the highest incidence of three-vessel disease, were older, had a worse Killip class, and had a higher prevalence of prior bypass surgery and heart failure. Patients presenting with ST-segment elevation or a combination of both ST-segment elevation/depression were more likely to be men and current smokers. [18] Those with T-wave inversion or ST-segment depression had a higher prevalence of hypercholesterolemia and hypertension, a longer history of coronary disease, and higher prevalence of previous angina, MI, angioplasty, or bypass surgery.[18] Furthermore, those with isolated T-wave inversion were most likely to have normal coronary arteries or insignificant coronary disease on coronary angiography. Those with ST-segment elevation or ST-segment elevation and depression were more likely to have single-vessel disease.

Of all four groups, those with isolated T-wave inversion had the lowest incidence of death or reinfarction ($p<0.001$) at 30 days followed by ST-segment elevation, then ST-depression, and finally, combined ST-segment elevation/depression. So, the ST-segment elevation and depression group had statistically significant higher rates of death or reinfarction than either ST elevation or ST depression alone.[18] Findings at six months were provocative since the group with ST-segment elevation/depression had the highest incidence of events ($p<0.001$). Lastly, the probability of early death (within 30 days after admission) was initially lower in the group with ST-segment depression but actually increased over time.

Savonitto and colleagues [18] concluded that early ECG allows for immediate bedside risk stratification in the ED. Early ECG was capable of distinguishing the risk of developing cardiac events for short-term and long-term follow-up. Patients with ST-segment elevation and depression tended to have the worse overall prognosis since they were at high risk for both early and late events. Although an older study, this study is frequently referenced in other articles about the prognostic value of ECG thus was included for review.

Boersma and colleagues [19] conducted a secondary analysis of the PURSUIT trial to determine the association between baseline characteristics and the 30-day incidence of death and the composite of death or myocardial reinfarction ((re) MI) in 9461 patients. Patients were eligible for the primary study if they presented to the ED within 24 hours of having chest pain (> 10 minutes) and had either transient ST-segment elevation (>0.5 mm), transient or persistent ST-segment depression (>0.5 mm), T-wave inversion (>1.0 mm) or elevated cardiac enzymes on their initial hospital ECG. Those with persistent ST-segment elevation (> 30 minutes) were excluded from the study.[19] One of the study's strengths was its inclusion of 726 hospitals in 28 countries, thus representing many different people and increasing the generalizability of its findings. ST-segment depression on the presenting ECG was strongly related with death as well as composite death/(re) MI endpoints at 30 days (OR 2.54 (95% 2.00-3.21), p<0.0001), a finding that is consistent with the other studies discussed.

Next, Mueller and colleagues [20] conducted a prospective cohort study 1) to determine the predictive value of ischemic ECG changes on clinical outcomes and 2) if early revascularization impacted adverse outcomes associated with ST-segment depression in patients with UA/NSTEMI. The sample of 1450 patients was stratified by the presence of ST-segment depression, T-wave inversion, or no changes on the admission ECG. Inclusion criteria were consecutive patients admitted with UA/NSTEMI and who underwent early invasive angiography between January 1996 and December 1999. Patients with new onset angina or angina with exertion were excluded. The primary dependent variable was all-cause mortality during index hospitalization and at follow-up up to 59 months. No power analysis or sample size justification was described. Patients had admission ECGs that were classified by the following: ST-segment depression defined as J-point depression ≥ 1mm followed by a horizontal or downsloping ST segment for at least 0.08 seconds. T-wave inversion was defined as T-wave deviation ≥ 1mm from baseline. Patients with both were classified as having ST-segment depression.[20]

Mueller and colleagues [20] concluded that both ST-segment depression and T-wave inversion on early admission ECG were independent predictors of long-term mortality. Similar to the sample characteristics previously reported by Savonitto and colleagues [18], patients with ST-segment depression on their admission ECG tended to be older and have three-vessel coronary artery disease as documented on angiography. The in-hospital mortality rate was 2.1% in patients with no ECG changes, 4% in patients with ST-segment depression ($p=0.02$), and 0.2% in patients with T-wave inversion ($p=0.02$). [20] Cumulative mortality at 36 months was 8% in patients with no ECG changes, 19.9% in patients with ST-segment depression, and 5.1% in patients with isolated T-wave inversion ($p=0.0001$). The hazard ratio for long-term mortality was 2.8 for patients with ST-segment depression ($p<0.001$) and 0.48 for T-wave inversion as compared to patients with no ECG abnormalities.

Grzybowski and colleagues [21] conducted a retrospective analysis to derive predictors of death in patients transported by ambulance with suspected myocardial infarction. They enrolled 253 subjects who presented with chest pain or shortness of breath. The primary dependent variable was death within seven days of ED arrival. The specific ECG indicators that were evaluated included ST-segment depression, T-wave inversion, left bundle branch block, other ST-segment abnormality, and anterior infarct location. While anterior infarct was defined as including ST-segment elevation of $\geq$0.1mV in two contiguous leads in V1-V4, the other ECG changes were not operationally defined which is a threat to construct validity of the study. None of the ECG predictors was statistically significant for death status within seven days of ED presentation.[21] However, trends revealed that having ST-segment depression or anterior infarct was more likely to be associated with death within a week. T-wave inversion actually seemed to be protective of death, which contrasts with the previous studies reported.

Initial Hospital ECG and Continuous ST-segment Monitoring

Two studies addressed whether the prognostic value of 12-lead ECG is enhanced with continuous ST segment monitoring. Patel and colleagues [22] conducted an observational study of 212 patients with unstable angina who were admitted to three different general hospitals in London. This was a secondary analysis of a randomized study that evaluated the use of heparin in addition to aspirin for this population. Each patient received an initial ECG on admission followed by 48 hours of continuous ST segment monitoring. Two observers who were blinded to any subsequent outcomes analyzed the initial ECG independently, thus contributing to the strengths of this study since blinding minimized potential bias. Significant ST depression was defined as ≥ 0.1 mV downsloping from baseline at 80 ms after the J point lasting for more than 60 seconds.[22] ST-segment elevation was defined as upward ST segment deviation of ≥ 0.2 mV at the J point.[22] ST segment depression on 12-lead ECG ($p=0.02$) and transient ischemia on continuous ECG monitoring ($p<0.001$) were predictive of non-fatal myocardial infarction or death. The presence of transient myocardial ischemia was the strongest independent predictor of outcome (OR 2.94 (95% CI 1.14-7.54), $p=0.025$). Patients with a normal admission ECG did not have adverse events (death or myocardial infarction). A normal admission ECG conferred a good prognosis ($p=0.076$).
These findings are both statistically and clinically significant, however findings are

limited to those with unstable angina.

Norgaard and colleagues [23] conducted a longitudinal study in 2004 to examine long term prognostic characteristics of continuous ST segment ECG monitoring in combination with 12-lead ECG risk indicators in patients with suspected ACS. The median follow up time for all patients was 28 months. They studied 213 patients with suspected ACS. The composite end point was death or reinfarction. Data were analyzed on an intention to treat basis, appropriate for longitudinal designs. Consistent with the findings by Patel [22], 12-lead ECG ST-segment depression at admission was a significant predictor of the composite end point of cardiac death and acute myocardial infarction (p=0.01). The sensitivity, specificity, and negative predictive value of one or more ST episodes in predicting death or MI at 30 days were 83%, 71%, and 99%. Long term, the sensitivity was only 53% while the specificity and negative predictive value were 72% and 88%.

Summary

Although the presence of acute ischemic changes on ECG is associated with a higher risk of cardiac events, the prognostic implications of different presentations of ECG abnormalities are not well defined. There have been several studies that have attempted to better understand the prognostic and predictive value of the initial hospital ECG, but only two have been conducted on ECG conducted in the pre-hospital setting. ST-segment depression is associated with a poor prognosis across all studies.

Gaps in the Literature

There are several gaps in current knowledge about PH ECG. Questions remain as to whether the PH ECG provides more useful diagnostic information beyond an initial hospital ECG obtained upon arrival to the ED. While a study by Kudenchuck and colleagues [5] found serial information between two ECGs to be helpful, there is limited knowledge about the specificity of PH ECG findings since ST-elevation confounders can mimic ST-elevation-myocardial infarction. The serial findings from this older study are intriguing and warrant further study since to date, no studies examine the implications of continuous ST segment monitoring in the pre-hospital setting. Second, although the presence of acute ischemic changes on ECG is associated with a higher risk of cardiac events, the prognostic implications of different presentations of ECG abnormalities are not well defined. Several studies have attempted to better understand the prognostic and predictive value of the initial hospital ECG, but only two [15, 16] have been conducted on ECG conducted in the pre-hospital setting.

Conclusion

In conclusion, numerous studies have shown that reporting or transmitting a PH ECG to the emergency department is an integral part of treatment for patients with ACS. The main benefit of PH ECG lies in its potential to reduce the overall time to administration of reperfusion therapy. Additionally, it enhances early arrival and triage to the emergency department and is associated with increased usage of reperfusion interventions, shortened time to treatment, and greater use of cardiac interventions. More research is needed to better understand the diagnostic accuracy and prognostic value of PH ECG.

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Table 1

Summary of Research Articles for Critical Literature Review (n=18)

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
Boersma et al. (2000) Predictors of Outcome in Patients With Acute Coronary Syndromes without Persistent ST-Segment Elevation *Circulation 101:2557-2567*	To determine relationship between baseline characteristics and occurrence of adverse events at 30-day	Secondary analysis (PURSUIT trial) CHR approved; unclear if consent required	N=9461 Presenting within 24h of episode of ischemic chest pain (>10 minutes), transient ST↑ Exclusion: Persistent (>30 min) ST↑	ST-segment elevation: >0.5mm ST-segment depression: >0.5mm T-wave inversion: >1.0mm Variables: age, heart rate, bp, ST↓, death and of death and/or recurrent MI	Logistic regression analysis Cubic spline functions Statistical significance: $p \leq 0.05$	Age, ST↓, rales/hx of heart failure, hr strongly related to death. Enrollment diagnosis: patients with MI had 50% increase in 30-day re-mi compared with UA History: Prior revascularization had better survival rate Previous bypass was associated w/ worse prognosis More events in Eastern Europe than North America	Strengths: Excellent description of statistical analyses; interactions considered amongst predictor variables Acknowledged interregional differences in applied treatment strategies for ACS (more PCI in North America than Eastern Europe) Included thorough discussion about clinical implications & proposed a scheme for clinical practice Limitations: data were previously collected
Brainard et al. (2005) The prehospital 12-lead ECG's effect on time to initiation of reperfusion therapy: a systematic review and metanalysis of existing literature *American Journal of Emergency Medicine 23:351-356*	To compare cardiac reperfusion times in patients with and without PH ECG	Systematic review, meta-analysis IRB not necessary Search terms: Emergency Medical Technician, Emergency Medical Service, Prehospital Care, Transportation of Patients, Ambulance, Cardiac	N = 99 Tx Gp (PH ECG)=54 Control Gp (No PH ECG)=45 Inclusion: must have control and intervention gps, symptom	Variables measured: symptom onset time-to-reperfusion	Means; medians 95% CI	*PH ECG Group:* 36.5 min (CI, 32.4-40.6) *No PH ECG Group:* 58.5 min (CI 56.1-60.9) Average unweighted difference of 22 min(CI 20.04-24)	Strengths: high quality studies (smaller variances, large sample size). Good discussion of literature search strategy. Limitations: Small combined total sample Lack of definition of reperfusion therapy (lytics versus PCI or

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
		Ischemia, Chest Pain, ST Segment, Electrodes, Myocardial Ischemia Coronary Care Nursing, Myocardial Infarction, Coronary Disease, ECG Monitoring, Physiologic	onset-to-reperfusion therapy				both), lack of operational definition for symptom onset
Canto et al. (1997) The Prehospital Electrocardiogram in Acute Myocardial Infarction: Is Its Full Potential Being Realized? *JACC 29(3):498-505.*	To compare characteristics and outcomes of patients with/without PH ECG	Retrospective, observational 6/94-4/96	Large, voluntary registry (National Registry of Myocardial Infarction 2) 1,388 hospitals included N=70,763 (3,768 or 5% with PH ECG) Inclusion: Patients presenting to hospital within 12-hours of AMI Exclusion: in-hospital infarction, transferred referrals, self-transported patients	PH ECG: Any ECG done before hospital arrival Symptom onset-to-hospital arrival Door-to-reperfusion (thrombolysis or PCI) Variables Baseline characteristics; median time from symptom onset to 1st ECG and hospital presentation; median time from hospital arrival to reperfusion therapy; proportion & modality of acute reperfusion therapy utilized; in-hospital interventions; clinical events including mortality	Chi-square for categorical variables. Wilcoxon rank sum for time intervals t-test for continuous variables Multiple logistic regression		Strengths: Large database; multi-center increases generalizability. Limitations: PH ECG validity & reliability issues since performed from multiple sources (medics, clinics, etc).

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
Curtis et al. (2006) The Pre-Hospital Electrocardiogram and Time to Reperfusion in Patients with Acute Myocardial Infarction 2000-2004 *JACC 47(8): 1544-52*	To determine effect of PH ECG on D2B time	Retrospective analysis (National Registry of MI-4) 1/2000-12/31/2002	AMI patients enrolled N=56,647 (divided into lytic cohort N=35,370 and PCI cohort N=21,277 for analysis <u>Inclusion</u> ICD dx AMI, CK or CKMB elevated, ECG evidence of AMI, nuclear med testing, echo, or autopsy evidence of AMI <u>Exclusion</u> No ST↑ or LBBB on initial ECG, transfer patients, AMI symptoms after admission, unknown symptom onset, no chest pain, initial ECG not diagnostic, missing, or >6 h after admission.	<u>Primary IV</u>: performance of PH ECG by EMS <u>DV</u>: Time between hospital arrival and and reperfusion therapy (lytic or PCI) Lytic cohort: hosp arrival to administration of lytic PCI cohort: hosp arrival to first balloon inflation Time-to-Guideline recommended therapy: Proportion of those who received lytics within 30 min. or PCI within 90 min. or prolonged group who received lytics >45 min or PCI >120 min. <u>Characteristics</u>: age, gender, insurance status, medical history (smoking, chronic renal insufficiency, previous AMI, HTN, family hx	Wilcoxon test for trend: to compare proportion of patients receiving a PH ECG in each year Hierarchical regression: Association between PH ECG and door to reperfusion time Chi-square test for overall proportions	<u>Use of PH ECG</u> 4.5% of lytic group; 8.0% of PCI group (rate increased slightly for both cohorts with each year of study) <u>Patient/hosp characteristics</u> Differences statistically significant (p<.01) =Table 1 pg 1548 <u>Sx onset-to-hosp arrival</u> *Lytic group*: PH ECG 83 min No PH ECG 95 min (p<.01) *PCI group*: PH ECG 80 min No PH ECG 103 min (p<.01) <u>Association of PH ECG w/ door-to-reperfusion time</u> *Lytic group*: PH ECG 24.6 min vs. No PH ECG 34.5 min (p<.01) *PCI group*: PH ECG 83.9 min vs. No PH ECG 107.7 min (p<.01) <u>Meeting Guideline time frames:</u> Greater proportion in PH	Strengths: More recent article comparable to Canto study. Large sample from national database. Reports on guideline recommended time frames, which has otherwise been limited. Similar group baseline characteristics. Findings clearly stated for each group. Limitations: Retrospective. Underlying theory is implicit. No power analysis discussed but adequate size. Threats to inter-rater reliability in ECG application. Symptom onset variable may be unreliable if patient report (not well defined here).

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
			PH ECG not performed by EMS or was obtained >1h before hosp arrival.	of AMI, hx of CAD, hypercholesterolemia, HF, previous PCI, CABG, initial ECG results, presenting hospital characteristics		ECG of both groups met recommended time frames ($p<.01$)	
Diercks et al (2009) Utilization and Impact of Pre-Hospital Electrocardiograms for Patients With Acute S-Segment Elevation Myocardial Infarction *JACC 53:161-166*	To determine the association of PH ECG and the timing of reperfusion therapy for STEMI	Prospective, observational 1/07-12/07 NCDR/ACTION Registry data IRB approval or quality assurance	N=12,097 (7,098 by EMS) Inclusion: Presenting to ACTION-participating hospitals with STEMI within 24h of symptom onset, self-transport or ambulance to ED Exclusion: Inter-hospital transfers, initial evaluation not in ED or cath lab	STEMI: persistent ST-segment elevation or new LBBB Variables: EMS data, medical hx, tx, in-hospital outcomes	Median values w/ interquartile ranges Wilcoxon rank-sum test Chi-square Logistic regression	1,941 (24.7%) received PH ECG PH ECG group had significant shorter D2N time, D2B time, met Guideline goals, use of acute medications PH ECG group had trend towards lower in-hosp mortality, HF, and shock	Strengths: Large study Controlled for confounders (time of day, time-to-first ECG) *construct validity* Limitations: No central core lab for ECG interpretation Selection bias since patients drawn from registry
Drew et al. (2011) A Simple Strategy Improves PH ECG Utilization and Hospital Treatment for Patients with ACS (ST SMART study)	To determine impact of PH ECG on scene time and time to intervention for ACS patients	Randomized clincal trial	N=794 Patients activating '911' for symptoms of ACS	Universal criteria (2007) ST↑ @ j-pt $V_{2,3}\geq0.2$mV men, ≥0.15mV women Other leads: ≥0.1mV ST↓ @ j-pt	t-test,Mann-Whitney, survival analysis	74% patients w/ ACS sx had PH ECG transmitted Scene time sig longer in PH ECG group D2B shorter for	Strengths: RCT; 1st using ST-segment monitoring triggered ECG w/ reduced lead set Limitation: not enough power to detect differences

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
				≥0.05mV T-inv ≥0.1mV *must see in contiguous leads		STEMI in PH ECG group (NS); Door to drug shorter for STEMI, UA ($p<.05$)	
Eckstein et al. (2008) Impact of Paramedic Transport with Prehospital 12-Lead Electrocardiography on Door-to-Balloon Times for Patients with ST-Segment Elevation Myocardial Infarction *Prehospital Emergency Care. 13(2):203-206*	To determine the impact of PH ECG on door-to-balloon times for STEMI prior to an established STEMI system Hypothesis: Paramedic acquisition of PH ECG would allow for earlier identification of STEMI patients which would decrease door-to-balloon times and improve outcomes.	Retrospective study, 4 hospitals with PCI capability the EMS community 1/05-12/05 -All patients received PH ECG since ambulances were equipped with 12-lead ECG -IRB approved, no discussion of consent or waiver -Med records were reviewed -Data were collected on patients who dx as STEMI. -Patients were divided into "self transport group" and "EMS transport group" per med record.	N=234 Inclusion: Admit dx of STEMI and hosp discharge dx of AMI. Confirmation of admit dx by ED MD or cardiologist as documented in med record. Exclusion: Not explicit	STEMI: >1mm elevation in 2 contiguous leads Primary end-point: Time-to-balloon inflation defined as ED arrival (triage time) until inflation Secondary end-points: Hospital LOS	Wilcoxon-Mann-Whitney test	**No difference:** Age, gender, ethnicity of self-transport vs EMS transport groups. **Differences:** Median ED arrival to cardiac cath was 64 minutes (EMS group) vs. 77 minutes (self-transport group) ($p<.05$). Median door-to-balloon times were 95 minutes (EMS gp) vs. 108 minutes (self-transport group) but not statistically significant	Strengths: well established STEMI system Limitations: Retrospective study; Used EMS call report to determine who was STEMI, times abstracted from med records-lack of synchronization of clocks, included hospitals all part of established STEMI system which do not reflect the majority of hospitals in U.S.; exclusion criteria not explicitly stated
Grijseels et al. (1995) Pre-hospital triage of patients with suspected myocardial infarction *European Heart Journal, 16:325-332*	To evaluate algorithms for the improvement of pre-hospital triage of patients with suspected ACS To determine predictors in pre-hospital	Prospective 1/92-10/92	N=1005 Patients evaluated by general practitioner and sub-sequently transferred to hospital for ACS evaluation	ECG: Table 2 pg 327 Variables measured: age, sex, # hours since symptom onset, duration/location of pain, previous medical hx	Student t-test Chi-square Stepwise logistic regression Receiver operator curves for diagnostic accuracy	Previous algorithms applied in pre-hospital setting: universal decrease in diagnostic accuracy ROC demonstrated mediocre performance in pre-hospital setting	Strengths: large sample size. Reliability enhanced since same predictors, similar statistic tests, and endpoints utilized as previously developed algorithms Limitations: Conducted in Rotterdam which has a

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
	setting of ACS and develop a model		Involved EMS and 15 hospitals in Rotterdam Group 1: Normal ECG Group 2: Abnormal ECG Group 3: Extensive MI			Presence of an abnormal ECG was the most important predictor of ACS	different EMS system; may limit generalizeability in U.S.
Grzybowski et al. (2000) A prediction model for prehospital triage of patients with suspected cardiac ischemia *Journal of Electrocardiology 33:253-258*	To derive predictors of death in AMI pts transported by EMS	Retrospective	N=244 All AMI pts in 3 Detroit EDs between 1996-1997 who were transported by ambulance	I.V. Prehospital predictors: vital signs, ambulance run time, type of hospital D.V. Primary- Death within 7 days Secondary- MI, UA, cardiac arrest during index hosp	Mean, standard deviations Chi-square, odds ratio, multiple logistic regression $P \leq 0.05$ significant	Survivors at 7-days significantly younger than nonsurvivors Survivors spent 4.8 min less time in EMS vehicle than nonsurvivors ($p \leq .05$) and had overall response time 7.8 min less than nonsurvivors ($p \leq .01$). Survivors had lower hr, rr, but higher BP than nonsurvivors (strange finding) ECG data: no diff between survivors and nonsurvivors but ST↓ showed trend for more likely death at 7 days	Strengths: Findings were controlled for by age Limitations: Retrospective; The final N is unclear

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
Herlitz et al. (2002) Predicting a life-threatening disease and death among ambulance-transported patients with chest pain or other symptoms raising suspicion of an acute coronary syndrome *American Journal of Emergency Medicine 20(7):588-594*	To evaluate how to predict a life-threatening disease, death within 30 days and death within 1 year in an ambulance population with chest pain/anginal equivalent	Retrospective, observational 12/98-02/99	Consecutive patients transported by ambulance with CP/anginal equivalent to 2 hospitals (Goteberg, Germany)	Life-threatening dz: AMI, UA, pulmonary edema, ARF, aortic aneurysm, stroke	Pitman's nonparametric test, Fisher exact test Two-tailed tests, logistic regression analysis, odds ratio, 95% CI P<0.05 significant	Characteristics: life threatening dz patients older, male, higher prevalence of previous MI, symptoms of CP Admission ECG: associated with mortality at 30d, 1 yr & diagnosis of life threatening dz, ST↑ and ST↓ predicted death, all signs predicted life-threatening dz, ST↓ independent predictor of death	Strengths: interesting findings for triage/risk assessment, good tables Limitations: Retrospective, data obtained from EMS records, poor definitions of symptoms such as "bad condition," conducted in one community in Europe, no discussion of attrition
Ioannidis et al. (2001) Accuracy and clinical effect of out-of-hospital electrocardiography in the diagnosis of acute cardiac ischemia: A meta-analysis *Annals of Emergency Medicine 37(5):461-470*	To quantify evidence of diagnostic performance of PH ECG in dx of acute cardiac ischemia PH ECG vs Hosp ECG compared Also to evaluate out-of-hospital thrombolysis	Meta-analysis	N=7508 Subjects included in 11 different studies (randomized & non-randomized)	N/A	N/A	PH ECG has excellent diagnostic performance for AMI and good for ACI For ACI: sensitivity was 76% and specificity was 88%; OR 23 For AMI: sensitivity was 68%, specificity was 97%, and OR 104 Out-of-hosp thrombolysis shortens time-to-tx and improves short-term morality. No difference in mortality between	Strengths: Large sample Limitations: Different criteria for coronary ischemia and abnormal ECG findings created heterogeneity between sensitivity and specificity Different people interpreted the ECGs across all studies

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
						PH ECG and Hosp ECG gps No increase in scene time for PH ECG gp	
Kudenchuk et al. (1998) Utility of the Prehospital Electrocardiogram in Diagnosing Acute Coronary Syndromes: The Myocardial Infarction Triage and Intervention (MITI) Project *JACC 32:17-27*	To characterize frequency/evolution of early ECG changes and determine effectiveness of these changes in improving dx of ACS	Prospective, RCT 1/1988-2/1993 IRB approval, no discussion of consent or waiver	Patients transported by ambulance with symptoms concerning for ACS Divided into 2 groups: randomized to prehosp thrombolysis versus hospital thrombolysis	ST segment coding: $\geq$1mm, <1mm, or absent STEMI: $\geq$1 mm in $\geq$2 contiguous leads (in absence of LBBB or a ventricular rhythm), $\geq$4mm in setting of LVH ST-segment depression: $\geq$1mm horizontal or downsloping in $\geq$2 contiguous leads (in absence of LBBB or a ventricular rhythm) Q-wave: $\geq$40ms in $\geq$2 contiguous leads (in absence of LBBB or a ventricular rhythm)	Two-tailed Student t-test Sensitivity, specificity, and predictive accuracy of a positive test Hierarchic log linear model	Frequency of ST insig higher for thrombolysis gp Initial Hosp ECG: frequency of ST sig lower for thrombolysis gp Thromb gp: prevalence of ST , ST↓, t-wave decreased but q-wave increased between prehosp and hosp ECG Serial ECG changes: prehosp thrombolysis gp: ST more likely to resolve by hosp Hosp thrombolysis gp: those w/ ST <1mm on prehosp ECG progressed to >1mm by hosp adm Thrombolysis @ hosp gp: Nondiagnostic ST on prehosp ECG progressed to diagnostic proportions between prehosp and initial hosp ($p=0.02$)	Strengths: Large sample, ECG data analyzed by blinded readers, Findings well presented in tables Evaluated ECG characteristics on group who did not received prehosp thrombolytics (controlled for possible effects) Limitations: Baseline group characteristic differences (age and heart rate)/question randomization scheme Utilized serial prehosp and hosp ECG but no discussion if same electrodes used (reliability issues)

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
						Serial changes in non-thromb study gp: characteristics described and sig more ECG changes on ACS gp Predictive values found (p 20) Serial ECGs improved diagnostic sensitivity for AMI	
Mueller et al. (2004) Prognostic Value of the Admission Electrocardiogram in Patients with Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction Treated with Very Early Revascularization *The American Journal of Medicine 117:145-150*	To test whether the poor prognosis of ST↓ is improved in patients with NSTEMI/UA who received early reperfusion therapy. To define the importance of T-wave inversion To determine if prognostic effects of ST↓ and T-wave inversion differ by sex	Prospective 1996-1999 IRB approved Consent obtained	N=1450 Consecutive patients with UA/NSTEMI receiving early reperfusion therapy enrolled (Heart Center of Bad Krozingen) Exclusion criteria: new angina pectoris on exertion or worsening angina during exertion only	ST-segment depression ≥1mm horizontal or downsloping for at least 0.08 seconds T-wave inversion ≥1mm deviation from baseline Early revascularization: Coronary angiography at admission in patients with persistent chest pain; within 24h in patients without symptoms Primary endpoint: all-cause death	$P<0.05$ considered statistically significant ANOVA for comparison among groups Chi-square Cox proportional hazards regression Kaplan-Meier survival analysis	N = 1450 New ST↓ were older, more than 50% had 3V coronary dz on angiography T-wave inversion more likely to present with non-Q-wave MI and elevated troponin-T In-hosp mortality: 2.1% no ECG changes 4% w/ ST↓ 0.2% w/T-wave inversion 6 month mortality: 8.0% no ECG changes 19.9% w/ ST↓ 5.1% w/T-wave inversion	Strengths: Large cohort, consecutive patients (eliminates selection bias), long-term follow-up, unselected pts, Uniform revascularization strategy used (stent), Quantified the extent of CAD in all pts and included it as a covariable in analysis Innovative since looked at early revascularization for UA/NSTEMI. Usually this is done for STEMI only Better defined prognostic value associated w/ specific ECG changes Limitations: no power analysis discussed, one

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
						ST↓ and T-wave inversion independent predictors of long-term mortality	hosp site only, may not be generalizable.
Norgaard et al. (2004) Long term risk stratification of patients with acute coronary syndromes characteristics of troponin T testing and continuous ST segment monitoring *Heart 90:739-744*	To examine long term prognostic value of troponin T and continuous ST segment monitoring with 12 lead ECG risk indicators for ACS patients	Secondary analysis of (TRIM trial) Prospective, randomized, muticenter trial comparing inogatran and heparin IRB approved Informed consent	N=213 Unstable angina patients Inclusion: Symptoms within 24h of enrollment Exclusion: BBB, pacemaker, <16h continuous recording time	ST-depression or T wave inversion: ≥0.1mV in ≥2 contiguous leads Contiuous ST-vector magnitude (ST-VM) measured at J+20ms	Intention to treat analysis Mann-Whitney U test for continuous variables, Chi-square or Fisher's exact for categorical variables	Independent predictors of death: ≥65 age, ST↓ on admission ECG, ≥1 ST-VM episode ($p<0.05$) ≥1 ST-VM episodes had sensitivity, specificity, and negative predictive value 83, 71, & 99%	Strengths: Long-term follow-up (28 months), intention to treat analysis Limitations: limited to data collected by primary study
Patel et al. (1996) Early continuous ST segment monitoring in unstable angina: prognostic value additional to the clinical characteristics and the admission electrocardiogram *Heart, 75:222-228*	To determine if continuous ST segment monitoring provides any further prognostic information in addition to the admission ECG	Secondary analysis Admission 12-lead ECG done prior to entry to study followed by 48h of continuous ST segment monitoring Approved by hospital ethics committee	Three general hospitals recruited patients for the RCT. Inclusion criteria -30-75 years -presented within 24 hours of an episode of typical angina -informed consent obtained Exclusion criteria -prolonged	ST-segment depression: ≥0.1 mV downsloping at J+80, lasting for more than 60s ST-segment elevation: ≥0.2mV upward ST-segment deviation at J-point Each episode had to return to baseline for at least a minute to be counted as "discrete." Variables: frequency,	Chi-square for categorical variables Mann-Whitney U for continuous non-normally distributed data Fisher's exact $P<0.05$ considered statistically significant Univariate logistic regression	212 patients, 80% male Mean age 58.9 (range 30-77) Prior hx of MI in over 40% of patients 42.5% had new onset anginal symptoms Resting ECG 61 (28.8%) had normal resting ECG 59 (27.8%) had ST↓ (of these 17 (8.0%) had ≥0.1mV and 42 (19.8%) had	Strengths: Admission ECG analyzed by 2 different observers blinded to outcome; limits bias; Novel in consideration of continuous ST-segment monitoring w/ important findings: Lesser degrees of ST↓ have important prognostic value; previous studies only reported on ST↓ ≥0.1mV Normal admission ECG have favorable outcome Limitations: Findings

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
			CP -ST↑ -evolving Q-waves N=212 patients	duration, association with chest pain Outcomes: MI, refractory UA	Forward stepwise logistic regression	<0.1mV 18 ECGs had ST↑ of $\geq$0.1mV (however all but 1 were associated w/ q-waves or t-wave changes) 95 (44.8%) had biphasic or inverted t-waves 47 (22.2%) had pathological q-waves <u>Continuous monitoring</u> 132 episodes of ischemia (32 patients or 15.1%); 104 (78.7%) were silent ST↓ on resting ECG associated w/ greater frequency of MI or death ($p=0.015$) as was transient ST-segment shift ($p<0.001$) No episodes occurred in those with normal admission ECG ($p=0.06$); normal admission ECG conferred a good prognosis ($p=0.038$) t-wave changes had	limited to those with UA only

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
						no prognostic value	
Savonitto et al. (1999) Prognostic Value of the Admission Electrocardiogram in Acute Coronary Syndromes *JAMA 281(8): 707-713*	To determine prognostic value of various ECG presentations of acute myocardial ischemia	Secondary analysis Divided into 4 groups: 1. isolated T-wave changes 2. ST ≥0.05 mV in at least 2 contiguous leads 3. ST↓ >0.05mV in at least 2 contiguous leads 4. Both ST and ST↓	GUSTO-11b trial enrolled 12, 142 patients; Inclusion criteria -All reported symptoms of cardiac ischemia at rest within 12h of admission - Accompanyin g ECG signs of acute myocardial ischemia	ST-segment elevation or depression: >0.05mV t-wave inversion: >0.1mV Primary end-point for GUSTO IIb: 30 day composite of death and re-MI Secondary end-point: Death, re-MI, CABG/PCI, and 6-month composite of death/re-MI	Continuous variables presented as medians and 25th and 75th percentiles Discrete variables presented as frequencies and percentages Probabilities Multivariate logistic regression	Patients w/ ST or ST↓ more likely to be men and smokers. T-wave inversion/ST↓ higher prevalence of high cholesterol, htn, longer hx of CAD (by angina, MI, PCI, or CABG); 30 days-Had highest incidence of normal coronary arteries; 30d and 6 months-lowest incidence of combined endpoint than any of the other gps (p<.001) ST moderate incidence at both 30d and 6 months. Events occurred earlier ST↓ had highest incidence of 3-v dz; worst overall risk profile (older, worse Killip class, diabetes, prior CABG, hx of HF or 3-v dz). Highest combined end-point (p<.001) vs ST at 30d and 6-months. Events tended to occur later	Strengths: Large study sample of high risk subjects; Several countries involved _Limitations: ECG interpretation done by many different attending physicians; threat to inter-rater reliability, Electrode placement variability

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
						ST and ST↓ also had highest incidence of combined end-point ($p<.001$) vs ST at 30d and 6-months	
Svensson et al. (2005) Prehospital identification of acute coronary syndrome/myocardial infarction in relation to ST elevation *International Journal of Cardiology 98:237-244*	To evaluate factors that identify ACS/AMI prior to hospital admission; develop predictors of necrosis in non ST-segment elevation	Prospective, observational	N=538 (511 independent patients) Consecutive patients with suspected ACS transported by ambulance (Stockholm, Sweden) Inclusion: CP ≥15 min within last 6h, dyspnea, or symptoms of ACS Exclusion: No criteria	ST-elevation: ≥2mm in leads V1-V4, ≥1mm leads V5-V6 ST-depression: ≥1mm in any lead	Descriptives (means, medians, percentages), Fisher's exact for dichotomous variables, stepwise logistic regression for predictors	ST-elevation: 88% developed AMI, 95% ACS No ST-elevation: 26% developed AMI, 56% ACS Simultaneous ST↓ associated with increased AMI or ACS dx. Independent predictors: male, ST↓, T-wave inversion, elevation of any biomarker, increasing age	Strengths: study flow very logical, well-organized article Limitations: no exclusion criteria which may threaten internal validity, potential violation of independence assumptions since patients with repeated visits were included in analyses, poor operational definitions (i.e. simulataneous leads, 'pale' symptom description
Zeymer et al. (2009) Reperfusion rate and inhospital mortality of patients with STEMI diagnosed already in the prehospital phase: results of the PREMIR study *Resuscitation 80:402-406*	To report characteristics about STEMI already diagnosed in the field 3/03-12/04	Prospective, descriptive study. Secondary analysis of PREMIR study Divided group for comparison by 1) Total gp N=2108 2) No reperfusion therapy gp N=377 3) Inhosp lytic gp N=273 4)PH lytic gp N=504 5)PH lytic + early	Consecutive STEMI patients transported by ambulance to the hospital. 64 emergency systems in Germany were included. N=2326 (218 excluded for CPR)	STEMI: Must have presence of 2 of the following criteria: Persistent angina for ≥20 min and ST↑ in 2 contiguous leads (≥1mm limb leads and ≥2mm precordial leads) or LBBB and elevation of CK-	Two-tailed Wilcoxon rank sum test: nonparametric test to compare continuous variables Odds ratio/confidence intervals Propensity score	N=2108 Symptom onset-to-PH ECG 85 min. PH ECG-to-PH lytics 10 min PH ECG-to-inhosp lytics 52 min PH ECG-to-PCI 86 min	Strengths: Large sample. Multiple hospital systems which increases the generalizability. Limitations: Underlying theory implicit. No power analysis discussed. Difficult to discern difference in Table 4 between PH lytic group (n=504) and PH

Citation	Purpose/ Aims	Design/ Methods	Sample/ Setting	Variables defined	Measurement Analysis	Results	Strengths/ Limitations
		PCI N=286 6)	Inclusion Criteria: Patients who presented with chest pain/anginal equivalent >20 min within 24h after symptom onset. PH ECG with ST↑ in 2 contiguous leads ≥1mm limb leads and ≥2mm precordial leads. LBBB Exclusion criteria: neurotrauma patients, severe hypoxemia, parallel antipyretic treatment. 218 subjects excluded in this analysis d/t CPR	MB or troponin. Antithrombotic therapy in PH phase: aspirin, clopidogrel, GP IIb/IIIa inhibitor, unfractionated heparin, low molecular weight heparin. Reinfarction: recurrent angina with re-elevation of CK-MB or angiographic demonstration of occlusion of infarct vessel Stroke: occurrence of persistent specific neurologic deficits. Major bleeding: any intracranial bleeding, bleeding w/ need for transfusion, or any other clinically relevant bleeding w/ need for intervention		49% primary PCI gp received treatment within Guideline Recommendations 88% of STEMI received early reperfusion	lytic alone gp (n=218).

Table 2

Common Abbreviations Used in Summary Table

Abbreviation	
ACS	acute coronary syndrome
AMI	acute myocardial infarction
BP	blood pressure
CCL	cardiac catheterization laboratory
D2B	door to Balloon Time
ED	emergency Department
EMS	emergency medical services
HR	heart rate
LBBB	left bundle branch block
LOS	length of stay
LVH	left ventricular hypertrophy
NSTEMI	non ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
PH ECG	pre-hospital electrocardiogram
ReMI	Reinfarction
STEMI	ST-elevation myocardial infarction
UA	unstable angina

Chapter 3

Pre-hospital 12-Lead ST-Segment Monitoring Improves the Early Diagnosis of

Acute Coronary Syndrome

Abstract

Background: Pre-hospital ECG (PH ECG) is becoming the standard of care for patients activating emergency medical services (EMS) for symptoms of acute coronary syndrome (ACS). Little is known about the diagnostic accuracy of ECG acquired by ST-segment monitoring in the pre-hospital setting.

Methods: We studied 620 patients who activated '911' for chest pain symptoms to determine the sensitivity and specificity of 12-lead ECG ST-segment monitoring in the pre-hospital period (PH ECG) for diagnosing ACS, and to assess whether the addition of PH ECG signs of ischemia/injury to the initial hospital 12-lead ECG obtained in the emergency department (ED) would improve the diagnosis of ACS.

Results: The sensitivity and specificity of the PH ECG were 65.4% and 66.4%. There was a significant increase in sensitivity (80%) and decrease in specificity (61%) when considered in conjunction with the initial hospital ECG ($p<0.001$). Those with PH ECG ischemia/injury were more than 2.5 times likely to have an ACS diagnosis than those who had no PH ECG ischemia/injury ($p<0.001$).

Conclusions: PH ECG data obtained with 12-lead ST-segment monitoring provides diagnostic information about ACS above and beyond the initial hospital ECG.

Introduction

Recent American Heart Association guidelines recommend acquisition of a pre-hospital electrocardiogram (PH ECG) for all patients with symptoms of acute coronary syndrome (ACS) who are transported by ambulance to the emergency department (ED).[1] Transmitting a PH ECG to the ED has the potential to facilitate earlier diagnosis and reduce time to treatment for patients with ACS.[2-5] The standard 12-lead ECG is the gold standard for electrocardiographic detection of acute myocardial ischemia/injury and is reported to be the single most important method to rapidly identify ACS in the ED.[6] However, the standard ECG has limited sensitivity (30%-70%) and specificity (70%-95%)[4,5,7-9] that results in 2% to 5% of patients with ACS being erroneously discharged from the ED, and 70% of patients admitted for suspect ACS not having it.[7]

There is little information about the diagnostic value of ECGs triggered by ST-segment monitoring that have been acquired in the pre-hospital setting. Therefore, the aims of this analysis of 12-lead ST-segment monitoring PH ECG data were to: 1) determine the sensitivity and specificity of one or more PH ECGs for diagnosing ACS, and 2) determine whether PH ECG data in conjunction with the initial hospital ECG improves diagnostic accuracy for ACS.

Methods

Data for this analysis were obtained from the ST SMART (Synthesized Twelve-lead ST Monitoring and Real-time Tele-electrocardiography) Trial, a prospective randomized clinical trial in Santa Cruz County, California. Santa Cruz County is a large county that includes both urban and rural areas. The total population is estimated to be about 250,000 persons, of which half live in rural coastal mountain areas serviced by winding roads, resulting in long pre-hospital transport times (median ‘911’ to hospital time, 40 minutes). There are two hospitals and a total of 26 emergency vehicles serving the entire county.

The primary aims of the ST SMART Trial were to compare patients with and without PH ECG in paramedic scene time, hospital time to treatment, and survival over the period of the study.[10] Patients were enrolled in the study from 2003 to 2008 and underwent follow-up for up to 4 years. Enrollment for the study occurred 7 days a week, 24 hours a day. Paramedics in the field were trained to identify all persons 30 years of age and older who activated 911 with complaints of non-traumatic chest pain, anginal equivalent symptoms such as new onset shortness of breath (not due to chronic lung disease or asthma), and syncope (not due to drug overdose or intoxication). Paramedics initiated special 12-lead ST-segment monitoring and automatic mobile telephone transmission software. The Institutional Review Boards at the University of California, San Francisco, and the participating hospitals approved the study. A waiver of patient consent in the field was granted to avoid delays in patients reaching the hospital. Community consent was obtained by placing notices in country newspapers (including a Spanish-language publication) and by posting information on the hospitals’ and the Emergency Medical System (EMS) agencies’ websites.[10] Research nurses obtained written consent from patients meeting inclusion criteria after admission to the ED.

The ECGs analyzed in the present analysis included all those acquired and stored in the pre-hospital ECG device as well as the initial hospital-acquired ECG. There were a total of 794 patients enrolled in the ST SMART trial. Of 794 patients enrolled, a total of 115 patients were excluded from the analysis because of left bundle branch block

(LBBB), left ventricular hypertrophy (LVH), or ventricular paced rhythm, all known confounders of the ST segment.[11] An additional 59 patients were excluded because they were enrolled in the study more than once, resulting in a final cohort of 620 patients with accompanying ECGs analyzed for this analysis.

Electrocardiographic procedures

All 26 paramedic-staffed emergency vehicles responding to 911 calls in the county were equipped with special study-modified portable monitor-defibrillator devices (Lifepak12, Physio-Control, Redmond, Washington). The study device software enabled the following: 1) synthesis of a 12-lead ECG from five electrodes, 2) continuous measurement of ST amplitudes (J + 60 milliseconds) every 30 seconds in all 12 leads, and 3) automatic storage and transmission of an ECG to the destination ED if there was a change in ST amplitude of 0.2 mV in ≥ 1 lead or 0.1mV in ≥ 2 contiguous leads lasting 2.5 minutes.[10] The portable monitor-defibrillator study device collected 20 seconds of electrocardiographic data and then selected the 10 seconds with the best signal-to-noise ratio to develop a noise-free median beat from which all 12-lead ST-segment measurements were obtained. If the initial 20 second sample was noisy, the device automatically analyzed the subsequent 20 seconds of data.[10] All county paramedics were taught to apply the 5 electrodes and manually initiate transmission of the initial PH ECG for patients with ACS symptoms.[10] Any subsequent ST-event PH ECGs were transmitted automatically without paramedic decision-making. To ensure successful PH ECG transmissions, the device automatically redialed up to 3 attempts if the EMS vehicle was in a location where mobile telephone communication was unavailable. The study device used a bandwidth of 0.05 to 150 Hz, which is the filtering recommended for diagnostic standard 12-lead ECGs.[10] A previous validation study determined a high percentage of agreement between the synthesized PH ECG and standard 12-lead ECG.[12]

All PH ECG data were stored electronically in a central computer and analyzed offline (CodeStat Suite version 8.0, Physio-Control, Redmond, Washington). All ECGs were manually read by the investigator [JZH] using the universal criteria for the diagnosis of ACS defined by the European Society of Cardiology and American College of Cardiology Committee.[9] An expert [CES] conducted random audits of ECG analysis to confirm the diagnosis of ACS and establish inter-rater reliability. Universal criteria were developed to increase the sensitivity and specificity of the ECG for ACS by recognizing gender and lead differences. They include the following:

New ST elevation at the J point in two contiguous leads with the cut-off points:

$\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V_2 through V_3 and/or $\geq$ 0.1 mV in other leads.

New horizontal or down-sloping ST depression $\geq$ 0.5 mV in two contiguous leads; and/or T inversion $\geq$ 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio >1.

The American College of Cardiology key data elements for measuring clinical management and outcomes of patients with ACS were used to define study variables (final diagnosis) and patient characteristics (demographics, cardiac history, coronary risk factors).[13] Patients were assigned a final diagnosis based on their initial hospital ECG analysis, biomarker evidence of necrosis, and medical record review. ACS diagnoses were classified as 1) STEMI, 2) NSTEMI, 3) MI of uncertain type, and 4) unstable angina. Unstable angina was further subcategorized into 1) Definite/probable unstable angina or, 2) possible unstable angina. Of these, only the subcategory of Definite/probable unstable angina was included in the ACS cohort for this analysis.

Statistical analysis

All data analyses were performed with SPSS software, version 17.0. Descriptive statistics were used to report demographic and clinical information. ECG signs of ischemia/injury (ST elevation, ST depression, T-wave inversion) were collapsed into dichotomous variables for analysis (ACS diagnosis yes/no) to calculate sensitivity, specificity, and positive/negative predictive values.

Logistic regression analysis was used to determine if PH ECG evidence of ischemia/injury added to the initial hospital ECG improved the ability to predict a diagnosis of ACS. In this regression, the dependent variable was ACS diagnosis yes/no. In the first step, a variable for the initial hospital ECG was entered to determine how well it predicted an ACS diagnosis by itself. In the second step, a variable for PH ECG was entered. Odds ratios with 95% CIs were calculated. The Omnibus Test of Model Coefficients was used to assess the fit of the final model. A P value of $<.05$ was adopted as the critical value to determine whether there were statistically significant differences between groups.

Results

Subject characteristics

A total of 620 consecutively enrolled patients were included in this analysis. Average age was nearly 70 years, with slightly more male predominance (Table 1). Ethnicity included 92% White, 3% Latino, 2% Asian, 1% Black, and 2% mixed or unknown. A history of hypertension was common, and one third of patients either currently smoked or had a history of smoking. There were 179 patients (28.9%) with a final ACS diagnosis (Table 2).

Sensitivity and Specificity

The sensitivity and specificity of the PH ECG for a diagnosis of ACS was determined to be 65.4% and 66.4%, respectively. There was a significant increase in sensitivity with a reduction in specificity when both the PH ECG and standard ECG were considered together (Table 3). Specifically, the sensitivity increased to nearly 80% while the specificity decreased to 61% when *either* the PH ECG or the initial hospital ECG had evidence of myocardial ischemia/injury. Figure 1 shows an example of the dynamic change between a PH ECG and initial hospital ECG.

The positive predictive value of the PH ECG was determined to be 68%, indicating that of those predicted to have an ACS diagnosis, the model accurately identified 68% of them. The negative predictive value was 80%, which means the model accurately identified 80% of those predicted not to have an ACS diagnosis.

Predictor of ACS

PH ECG evidence of ischemia/injury was an independent predictor for an ACS diagnosis. Moreover, adding PH ECG evidence of ischemia/injury to the initial hospital ECG significantly improved the overall model fit ($p<0.001$), making the model a better predictor for an ACS diagnosis when PH ECG ischemia was included than initial hospital ECG data alone (Table 4).

Discussion

To our knowledge, this study is the first to report improved sensitivity (nearly 80%) of the ECG for an ACS diagnosis when using ST-segment monitoring-triggered ECGs from the field in conjunction with the initial hospital ECG. The dynamic ST-segment changes between pre-hospital and hospital ECGs were a critical discriminator for an ACS diagnosis. Our findings are in agreement with a study conducted by Kudenchuk and colleagues [5] who reported that when serial ST/T changes between a PH ECG and hospital ECG were considered, the sensitivity significantly increased from 80% to 87%, with a reduction in specificity from 60% to 50%.[5] Unlike our study that utilized ST-segment triggered PH ECG, Kudenchuk and colleagues [5] evaluated a conventional 12-lead PH ECG obtained by paramedics in the ambulance. A likely explanation for Kudenchak et al's higher sensitivity and lower specificity compared with our results is that they included any sign of ischemic abnormality, not just that for acute ischemia/injury. However, both studies confirm that serial ECG recordings enhance the diagnostic sensitivity for ACS, as compared to a single tracing.

We also found that PH ECG evidence of ischemia/injury is a significant independent predictor of an ACS diagnosis. Those with PH ECG ischemia were 2.5 times more likely to have an ACS diagnosis than those without PH ECG ischemia/injury. In addition, adding PH ECG evidence of ischemia/injury to a model containing the initial hospital ECG significantly improved the ability to predict an ACS diagnosis. Two studies have evaluated the diagnostic value of an ECG in the pre-hospital setting. Grijseels and colleagues [14] conducted a study to evaluate five previously developed algorithms for the diagnosis of ACS in the pre-hospital setting. They reported the sensitivity (43%-77%) and specificity (38%-78%) of the five algorithms and found the presence of various ECG abnormalities in the pre-hospital setting to be most predictive of an ACS diagnosis.[14] Specific ECG abnormalities included ventricular rhythm, pacemaker rhythm, presence of Q-waves, right or left bundle branch block, LVH, or ECG signs of ischemia/injury. Unlike our study that represented patients contacting '911' for symptoms of ACS, this study included patients who were referred to the ED from a general practitioner's office. In 2005, Svensson and colleagues [15] examined a cohort of patients similar to ours who activated EMS for symptoms of ACS. They reported on the predictive ability of specific ECG signs of ischemia/injury (ST elevation, ST depression, T-wave inversion) found on a PH ECG for an ACS diagnosis. They determined the presence of ST depression had the highest independent predictive value for an ACS diagnosis (OR 2.62, 1.23-5.58, $p<0.05$).[15] Both of these previous investigations by Grijseels [14] and Svensson [15] differed from our study in that they examined the effects of a *single* "snapshot" 12-lead PH ECG rather than multiple PH ECGs triggered by ST-segment monitoring.

Limitations

This study was a secondary analysis so data collection methods, inclusion/exclusion criteria, and collected variables were all predetermined. PH ECGs were recorded using a 5- electrode reduced lead configuration that was specifically developed for the ST SMART study. It is important to consider that different methods of ECG acquisition can result in different ST/T wave morphologies, and therefore should be interpreted with caution. Although the validation study determined that the synthesized PH ECG was comparable to the hospital ECG for diagnosis of ischemia/injury, the validation study did not assess diagnostic agreement for LVH. For this reason, we confirmed the diagnosis in all patients with criteria for LVH on their PH ECG by reviewing the hospital ECGs.

Conclusions

PH ECG data obtained with 12-lead ST-segment monitoring provides information above and beyond the initial hospital ECG obtained in the ED. PH ECG enhances the diagnostic sensitivity for ACS and helps to predict ACS in an early phase of emergency cardiac care.

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Table 1

Baseline Sample Characteristics (n=620)

Variable	
Age	69.77 ± 14.5
Male gender	320 (52%)
Past Medical History	
Smoker	211 (34%)
Diabetes	131 (21%)
Hypertension	381 (62%)
History of MI	118 (19%)
History of CAD	194 (31%)
History of Angina Pectoris	184 (30%)

MI = myocardial infarction
CAD = coronary artery disease

Table 2

Subjects with a Final Diagnosis of Acute Coronary Syndrome (n=179)

Diagnosis	n (%)
STEMI	47(26.3)
NSTEMI	54(30.2)
MI of unknown origin	1(0.5)
Definite/probable UA	77(43)

ACS = acute coronary syndrome
STEMI = ST-elevation myocardial infarction
NSTEMI = non ST-elevation myocardial infarction
UA = unstable angina

Table 3

Sensitivity and Specificity of PH ECG Alone and in Conjunction with the Hospital ECG for an ACS diagnosis (n=620)

	PH ECG	PH or Hosp ECG ischemia	*P* value
Sensitivity	65.4%	79.9%	<.001
Specificity	66.4%	61.2%	<.001

McNemar Test

ACS = acute coronary syndrome
PH ECG = pre-hospital electrocardiogram
Hosp ECG = initial hospital electrocardiogram

Table 4

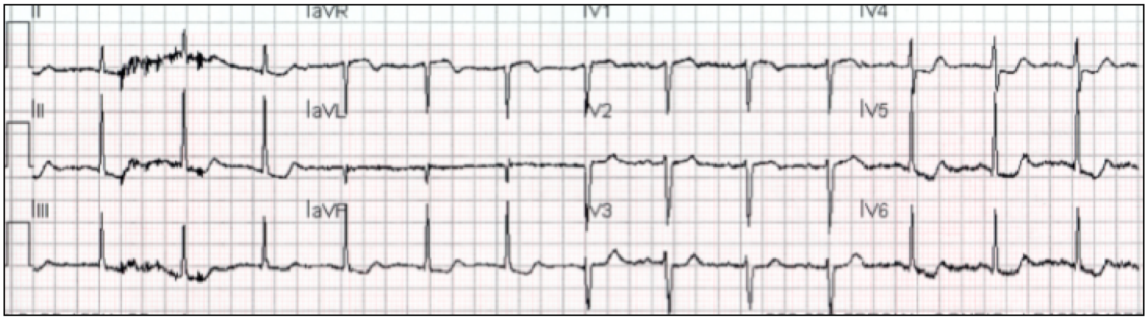
Logistic Regression Analysis for ECG Predictors of an ACS Diagnosis

Predictor variables	*P* value	Odds ratio	95% CI
Hospital ECG ischemia/injury	<.001	6.762	4.47-10.23
PH ECG ischemia/injury	<.001	2.543	1.70-3.80

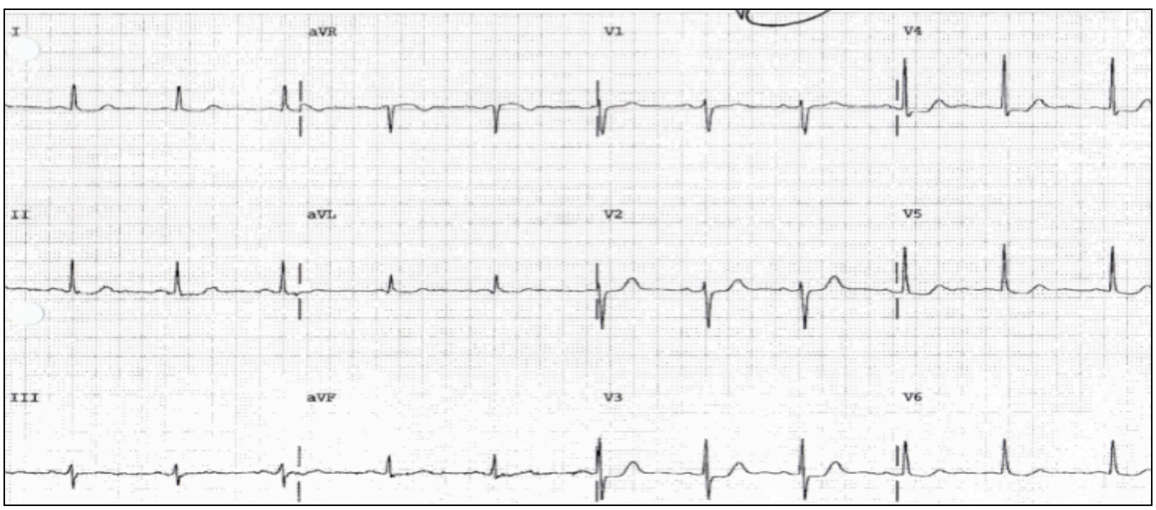
Omnibus Tests of Model Coefficients $\chi^2(2) = 138.625$, $p < .001$

Figure 1

a. PH ECG evidence of ischemia. Note widespread ST depression in leads II, III, aVF, $V_{4\text{-}6}$.



b. The same patient shows no evidence of ischemia on the initial hospital ECG recorded 19 minutes later in the ED. However, on hospital day #2, coronary catheterization revealed left main disease and patient underwent coronary bypass surgery.



Chapter 4

Pre-hospital ECG Manifestations of Acute Myocardial Ischemia are an Independent Predictor of Adverse Hospital Outcomes

Abstract

Background: Pre-hospital ECG (PH ECG) is becoming the standard of care for patients activating emergency medical services (EMS) for symptoms of acute coronary syndrome (ACS). Little is known about the prognostic value of ischemia found on PH ECG.

Study Objectives: The purpose of this study was to determine whether manifestations of acute myocardial ischemia on the PH ECG are predictive of adverse hospital outcomes.

Methods: The study was a retrospective analysis of all PH ECGs recorded in 630 patients who called "911" for symptoms of ACS and were enrolled in a prospective clinical trial. ST-segment monitoring software was added to the PH ECG device with automatic storage and transmission of ECGs to the destination emergency department (ED). Patients' medical records were reviewed for adverse hospital outcomes.

Results In 630 patients who called "911" for ACS symptoms, 270 (42.9%) had PH ECG evidence of ischemia. Overall, 37% of patients with PH ECG ischemia had adverse hospital outcomes compared to 27% of patients without PH ECG ischemia ($p < .05$). Those with PH ECG ischemia were 1.55 times more likely to have adverse hospital outcomes than those without PH ECG ischemia (CI 1.09-2.21, $p<0.05$), after controlling for other predictors of adverse hospital outcomes (i.e. age, gender, medical history).

Conclusions: Evidence of PH ECG ischemia is an independent predictor of adverse hospital outcomes. ST segment monitoring in the pre-hospital setting may identify high-risk patients with symptoms of ACS and provide important prognostic information at presentation to the ED.

Introduction

The American Heart Association recommended acquisition of a pre-hospital ECG (PH ECG) for patients with symptoms of acute coronary syndrome (ACS) as a Class I recommendation (supported by strong evidence) in the 2000 Advanced Cardiac Life Support guidelines.[1] As a result, acquisition of a PH ECG is becoming the standard of care for patients who access emergency medical services (EMS) with suspected ACS. While past PH ECG investigations have focused on the reduction in time to reperfusion treatment in ST elevation myocardial infarction (STEMI), little is known about its prognostic value for adverse clinical outcomes. The primary aim of this study was to determine whether manifestations of acute myocardial ischemia on the PH ECG are associated with adverse hospital outcomes.

Methods

Data for this retrospective analysis were obtained from the ST SMART (Synthesized Twelve-lead ST Monitoring and Real-time Tele-electrocardiography) Trial, a prospective randomized clinical trial in Santa Cruz County, California [2] from 2003-2008. The primary aims of the ST SMART Trial were to compare patients with and without PH ECG ST-segment monitoring in paramedic scene time, hospital time to treatment, and survival over the period of the study.[2] Enrollment for the study occurred 7 days a week, 24 hours a day. Paramedics were trained to identify all persons 30 years of age and older who activated "911" with complaints of non-traumatic chest pain, anginal equivalent symptoms such as new onset shortness of breath (not due to asthma), or syncope (not due to drug overdose or intoxication).

The Institutional Review Boards at the University of California, San Francisco, and the two hospitals in the County approved the study with a waiver of consent in the field to avoid delays in patients reaching the hospital. Community consent was obtained by a front-page report in the county's newspaper (*Santa Cruz Sentinel, 2003)* and by information posted on hospitals' and EMS agencies' websites.[2] Research nurses obtained written consent from all study participants once they reached the hospital.

Electrocardiographic procedures

All 26 paramedic-staffed emergency vehicles responding to 911 calls in the county were equipped with specially designed portable monitor-defibrillator devices (Lifepak12, Physio-Control, Redmond, Washington). The study device software enabled the following: 1) synthesis of a 12-lead ECG from five electrodes, 2) measurement of ST amplitudes (J+60 milliseconds) every 30 seconds in all 12 leads, and 3) automatic storage and transmission of an ECG to the destination ED if there was a change in ST amplitude of 0.2 mV in 1 lead or 0.1 mV in $\geq$ 2 contiguous leads lasting 2.5 minutes.[2]

The study device used a bandwidth of 0.05 to 150 Hz, which is the filtering recommended for diagnostic standard 12-lead ECGs.[2] A previous validation study determined a high percentage of agreement between the synthesized PH ECG and standard 12-lead ECG.[3] The portable monitor-defibrillator study device collected 20 seconds of electrocardiographic data and then selected the 10 seconds with the best signal-to-noise ratio to develop a noise-free median beat from which all 12-lead ST-segment measurements were obtained. If the initial 20-second sample was noisy, the device automatically analyzed the subsequent 20 seconds of data.[2]

All county paramedics (n=80) were taught to apply the 5 electrodes and manually transmit an initial PH ECG for patients with ACS symptoms.[2] This initial manual ECG transmission activated the study ST-segment monitoring software. Any subsequent ST-event PH ECGs were transmitted automatically without paramedic decision-making. To ensure successful PH ECG transmissions, the device automatically redialed up to 3 attempts if the EMS vehicle was in a location where mobile telephone communication was unavailable.

PH ECG data were stored in the device and analyzed offline (CodeStat Suite version 8.0, Physio-Control, Redmond, Washington). PH ECGs were manually read by the investigator [JZH] using the universal criteria for the diagnosis of ACS defined by the European Society of Cardiology and American College of Cardiology Committee.[4] An expert [CES] conducted random audits of ECG analysis to confirm the diagnosis of ACS and establish inter-rater reliability. The revised criteria were developed to improve the sensitivity and specificity of the ECG by recognizing gender and lead differences. They include: 1) ST segment elevation at the J-point with cut-off points $\geq$ 0.2 mV in men and $\geq$ 0.15 mV in women in leads V_2 and V_3 or $\geq$ 0.1mV in other leads; 2) horizontal or down-sloping ST segment depression $\geq$ 0.05 mV or 3) T-wave inversion of $\geq$ 0.1 mV in leads with prominent R waves or R/S ratio >1. All ECG criteria had to be present in two contiguous leads.[4]

Research nurses obtained information about the occurrence of adverse hospital outcomes from hospital medical records. The American College of Cardiology key data elements for measuring clinical management and outcomes of patients with ACS were used to define hospital complication variables (Table 1) and patient characteristics (demographics, cardiac history, coronary risk factors).[5]

Statistical analysis

All analyses were conducted in SPSS statistical software (Version 17, Somers, NY). ECG signs of ischemia (ST elevation, ST depression, T-wave inversion) were collapsed into one dichotomous independent variable (PH ECG ischemia yes/no) for analysis. The nine individual hospital complication variables were combined into one dichotomous endpoint (adverse hospital outcomes yes/no) for analysis. Descriptive statistics were used to report baseline characteristics and clinical information. χ^2 statistical analyses were used to compare categorical variables. Logistic regression analysis was used to evaluate independent predictors of adverse hospital outcomes. The following independent variables were evaluated in the regression model: PH ECG evidence of ischemia, age, gender, history of MI, coronary artery disease (CAD), diabetes, hypertension, smoking, dyslipidemia, or family history of CAD. The dependent variable used in the regression model was the dichotomous endpoint of adverse hospital outcomes. A P value of <.05 was adopted as the critical value to determine whether there were statistically significant differences between groups.

Results

PH ECGs selected for analysis

The PH ECGs analyzed included all those acquired and stored in the pre-hospital ECG device in the ST SMART Trial. There were a total of 794 subjects with PH ECGs enrolled in the ST SMART trial. Of these, 105 patients were excluded from the present analysis with left bundle branch block (LBBB), left ventricular hypertrophy (LVH), or ventricular pacing rhythm since universal criteria for acute MI are to be applied only in the absence of these confounding conditions.[4] An additional 59 patients were excluded because they had been enrolled in the study previously, resulting in a final cohort of 630 patients for the present analysis.

Subject characteristics

The mean age of subjects was 69.77 years (SD 14.46) and 51.7% were male. Ethnicity included 91.7% white, 2.5% Latino, 0.6% black, and 5.2% mixed/unknown. Baseline sample characteristics including coronary risk factors and cardiac history are summarized in Table 2.

Of the total of 630 patients with ACS symptoms, 270 (42.9%) had PH ECG evidence of ischemia (54 with ST elevation, 175 with ST depression, and 41 with isolated T-wave inversion). There were 182 (28.9%) patients who had a discharge diagnosis of ACS that included the following: STEMI 48, NSTEMI 54, MI of unknown origin 1, and 79 with definite/probable unstable angina.

The group with manifestations of acute myocardial ischemia on their PH ECG had a significantly higher proportion of adverse hospital outcomes compared with the group without such ECG signs. Overall, 37% of patients with PH ECG ischemia had adverse hospital outcomes compared with 27% of the group without ($p<0.05$)(Table 3). Specifically, patients with PH ECG ischemia had more ventricular dysrhythmia requiring intervention (9.3 vs. 3.9%, $p<0.05$) and more atrial dysrhythmia requiring intervention (16.3% vs. 10.0%, $p<0.05$) than those without PH ECG ischemia. Furthermore, having PH ECG ischemia was associated with a trend towards more cardiogenic shock (3.7 vs. 1.1%, $p=0.05$).

As shown in Table 4, PH ECG ischemia was one of the strongest predictors for adverse hospital outcomes. Specifically, those with PH ECG ischemia were 1.55 times more likely to have adverse hospital outcomes than those without PH ECG ischemia, controlling for other factors in the model. The full model containing all predictors was statistically significant ($\chi^2 = 50.66$, $p<0.001$). The model as a whole explained between 7.8% (Cox & Snell R Square) and 10.9% (Nagelkerke R Square) of the variance of adverse hospital outcomes. Older age, hypertension, history of CAD, and smoking were also significant predictors of any adverse hospital outcomes.

Discussion

To our knowledge our study is the first to provide information about the prognostic value of ST-segment monitoring in the pre-hospital setting. Continuous ST segment monitoring combined with clinical criteria has been described as an effective method of identifying high-risk subsets in the early phase of ACS after hospital admission.[6] Our study shows that data obtained from ST-segment monitoring in the pre-hospital setting improves the ability to identify patients *earlier* at greater risk for adverse hospital outcomes. Earlier risk stratification may help high-risk patients by allowing for the institution of more aggressive therapies earlier, without subjecting lower risk patients to unnecessary treatment.

Our data showed that 42.9% of patients activating "911" for symptoms of ACS had evidence of ischemia in the pre-hospital setting, and these patients were at greater risk for adverse events during the course of their hospitalization than those without such PH ECG signs. Specifically, those with evidence of PH ECG ischemia had a higher incidence of adverse hospital outcomes compared to those without (37% vs. 27%, p<0.05). Moreover, we found that ischemia in the pre-hospital setting is an independent predictor of adverse hospital outcomes.

Patients presenting to the ED with ECG evidence of ischemia are at particular risk for cardiac death, non-fatal ischemic events, dysrhythmias, heart failure, stroke and major bleeding.[12] ST-T wave changes indicative of ischemia can predict myocardial infarction and subsequent development of life-threatening complications.[3-5] Our findings are in general agreement with previous studies that have found electrocardiographic evidence of ischemia on the initial hospital admission ECG to predict these adverse hospital outcomes.[7,8]

An early study by Brush and colleagues [8] studied the admission ECG to identify patients who could be safely hospitalized in an intermediate care unit. Those with evidence of ischemia had significantly higher incidences of life-threatening complications (ventricular fibrillation, sustained ventricular tachycardia, or heart block) than those without. Other complications (unsustained ventricular tachycardia, heart failure, third heart sound, jugular venous distension, cardiogenic shock, conduction disturbances, atrial dysrhythmias, or recurrent chest pain) were three to ten times more likely in those with ischemia versus those without ($p<0.01$).[8] Some differences from our study were that Brush et al.'s inclusion criteria were less stringent and included patients with LVH, LBBB, or paced rhythm. They also applied less sensitive ECG criteria and evaluated a single snapshot ten second admission ECG. We applied more recent universal criteria for ECG interpretation, which considers gender differences.[4]

Goldman et al. [7] conducted a large study to identify clinical factors that predicted which patients presenting with chest pain would have complications requiring intensive care. They analyzed the admission hospital ECG and found electrocardiographic abnormalities to be the most important predictor of major complications within the first 24 hours after hospital presentation.[7] Those with ischemia had significantly more dysrhythmia, pump failure, and recurring ischemia than those without ischemia. This study like the prior one by Brush et al. [8] examined the prognostic value of a single admission ECG to determine patients at risk of complications, versus PH ECG obtained with ST segment monitoring. The sample population of these studies [7,8] was similar since they evaluated consecutive patients presenting to the ED with chest pain, although different from ours since all patients arrived by ambulance.

A more recent study by Pelter et al. [9] examined the prognostic value of continuous ST-segment monitoring for patients admitted with ACS in determining adverse hospital outcomes.[9] Similar to our findings, investigators found that transient myocardial ischemia was an independent predictor for adverse hospital outcomes. Pelter et al. reported that 46% of patients with ischemia had adverse hospital outcomes which included dysrhythmias, shock, pulmonary edema, acute MI after admission, abrupt closure after percutaneous coronary intervention, transfer to intensive care unit, or death.[9] A difference from our study was that these patients were all admitted and treated for a confirmed ACS diagnosis whereas our sample population included all those with symptoms of ACS activating EMS.

Limitations

Our study has potential limitations that should be considered. First, this study was a secondary analysis so data collection methods, inclusion/exclusion criteria, and collected variables were all predetermined. Second, our study was not powered to reliably examine the association of PH ECG ischemia on all-cause mortality. Lastly, PH ECGs were recorded using a 5-electrode reduced lead configuration that was specifically developed for the ST SMART study. It is important to consider that different methods of ECG acquisition can result in different ST/T wave morphologies, and therefore should be interpreted with caution.

Conclusions

ST-segment monitoring used in the pre-hospital setting may provide better risk stratification in patients activating "911" with cardiac symptoms. Future research is needed to determine whether earlier diagnosis of acute myocardial ischemia in the pre-hospital phase of ACS will result in improved patient survival and quality of life.

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Table 1

Adverse Hospital Outcomes

1. Death 2. AMI distinct from the admission event 3. Recurrent rest angina with ECG changes 4. Recurrent rest angina without ECG changes 5. Heart failure that developed after hospital admission 6. Cardiogenic shock 7. Atrial dysrhythmia requiring intervention 8. Ventricular dysrhythmia requiring intervention 9. High-degree atrio-ventricular block (third degree block or second-degree block with bradycardia requiring pacing)

AMI = acute myocardial infarction

Table 2

Baseline Sample Characteristics (n=630)

Age	69.77 (±14.46)
Male Gender	326 (51.7%)
Race	
White	578(91.7%)
American Indian/Alaskan Native	16 (2.5%)
Asian	14 (2.2%)
Black	4 (0.6%)
Unknown	18 (3.0%)
Past Medical History	
Hypertension	390(61.9%)
Dyslipidemia	247(39.3%)
Smoker (current, former, or recent)	214 (34.0%)
History of CAD	197(31.3%)
Diabetes	135(21.4%)
History of MI	120(19%)
Angina pectoris	185(29.5%)
PCI	109(17.3%)
CABG	76(12.1%)
Family History of CAD	96(15.3%)

CAD = coronary artery disease
MI = myocardial infarction
PCI = percutaneous coronary intervention
CABG = coronary artery bypass graf

Table 3
Frequencies of Adverse Hospital Outcomes Comparing Patients With and Without PH ECG ischemia (n=630)

Adverse hospital outcomes	PH ECG ischemia n(%)	Without PH ECG ischemia n(%)	*P* value
Death	3(1.1)	4(1.1)	1.000
MI	5(1.9)	3(0.8)	0.269
Angina with ECG changes	4(1.5)	1(0.3)	0.111
Angina without ECG changes	14(5.2)	18(5.0)	1.000
New heart failure	41(15.2)	44(12.3)	0.176
Shock	10(3.7)	4(1.1)	0.05
Atrial dysrhythmia*	44(16.3)	36(10.0)	**0.022**
Ventricular dysrhythmia*	25(9.3)	14(3.9)	**0.005**
AV block	12(4.4)	8(2.2)	0.222
Adverse hospital outcomes	99(36.7)	98(27.2)	**0.007**

* Requiring urgent intervention

Table 4

Logistic Regression Analysis on Predictors of any Adverse Hospital Outcomes (n=630)

Predictor variables	Odds ratio (95% CI)	*P* value
Dependent variable: adverse hospital outcomes		
PH ECG ischemia	1.55(1.09-2.21)	**0.016**
Gender	0.82(0.57-1.18)	0.287
Age	1.02(1.00-1.03)	**0.01**
History of MI	0.87(0.53-1.44)	0.60
History of CAD	1.69(1.085-2.631)	**0.02**
Diabetes	1.30 (0.85-1.97)	0.228
Hypertension	1.64(1.10-2.44)	**0.015**
History of Smoking	1.49(1.02-2.16)	**0.04**
History of Dyslipidemia	1.10(0.76-1.60)	0.613
Family History of CAD	0.58(0.34-0.99)	0.05

Omnibus Tests of Model Coefficients $\chi^2(10) = 50.663$, $p < .001$

CI = confidence interval
MI = myocardial infarction
CAD = coronary artery disease

Chapter 5

Conclusion

The overall purpose of this dissertation was to gain more understanding about the diagnostic and prognostic abilities of pre-hospital electrocardiography (PH ECG) triggered by ST-segment monitoring for the management of acute coronary syndrome (ACS). The findings from the presented studies make significant contributions to the current body of knowledge about PH ECG and its role in cardiac systems of care. Specifically this research provides new information about the diagnostic accuracy of PH ECG triggered by ST-segment monitoring, and offers novel insight into the association of PH ECG ischemia and clinical outcomes.

The first research study (chapter 3) provides evidence that PH ECG acquired by ST-segment monitoring with a reduced lead set configuration can accurately identify ischemia in the pre-hospital setting. Findings support a role for serial ECG monitoring in the early phases of ACS management, since the diagnostic accuracy for ACS was significantly improved when PH ECG data were considered in conjunction with initial ECG data acquired in the emergency department (ED). This is the first study to determine the sensitivity and specificity of PH ECG triggered by ST-segment monitoring, and to demonstrate improved diagnostic accuracy using continuous ST-segment monitoring triggered ECGs in the pre-hospital setting. We also found that PH ECG evidence of ischemia/injury is a significant predictor for an ACS diagnosis. The second research study (chapter 4) focuses on the impact of PH ECG manifestations of ischemia on clinical outcomes. The study shows that patients with PH ECG evidence of ischemia are at a greater risk for adverse hospital events. Moreover, evidence of PH ECG ischemia is an independent predictor of adverse hospital outcomes. This study is novel since the actual ECG signs of ischemia on ST-segment monitored PH ECG were examined, unlike previous studies that made conclusions based on whether a patient received PH ECG or not [1]. It is also the first to determine the prognostic value of PH ECG data obtained from ST-segment monitoring.

Limitations/Strengths

There are several limitations in the present study that should be noted. First, this was a secondary analysis so all data collection methods, inclusion/exclusion criteria, study variables, and the quality of the data were predetermined. Missing PH ECG data due to artifact or noise is an example of the limitations due to data previously acquired in the parent study. Despite the rigorous training given to paramedics in an effort to obtain valid PH ECG data, there were many ECG tracings that were non-analyzable due to artifact or noise. Such artifact is inevitable since the pre-hospital setting is often chaotic, uncontrolled, and monitoring occurs during transport, but this threatens the reliability of PH ECG data in this secondary analysis. Miscellaneous technical issues with mobile phone transmission during data collection were another threat to the reliability of PH ECG data. Reported reasons for poor transmission include poor transmission pathways, especially during peak hours of use; lack of proximity of the EMS unit to a cellular telephone cell, simultaneous transmission of 12-lead PH ECGs to the same receiving stations by two separate EMS units, and operator error [2]. Terkelsen et al [3] reported that up to 20-40% of transmission failures may occur due to wireless "dead zones" in a moving ambulance or in rural areas with sparse coverage, certainly potential concerns for the reliability of PH ECG data in this study.

Findings may have limited generalizability since enrollment was restricted to two community hospitals in a rural county, and the population consisted primarily of white patients so may not be applicable to other races. Another important limitation to be considered is the difference in how the PH ECG and the initial hospital ECG were acquired. As mentioned previously, PH ECGs were recorded using a 5-electrode reduced lead configuration that was specifically developed for the parent study, while hospital ECG data were acquired with a standard 12-lead configuration. Although the synthesized 12-lead ECG was validated in a previous study [4], different methods of ECG acquisition can result in different ST segment morphologies. In the first study (chapter 3), both PH ECGs and initial hospital 12-lead ECGs were analyzed and compared to determine diagnostic accuracy. This is not optimal, since a 12-lead ECG should only be compared to another 12-lead ECG for diagnostic purposes. Another potential limitation to consider is the differences in accurate ECG recordings between the PH ECGs and hospital ECGs. Correct and standardized placement of electrodes is crucial for accurate ECG recording of myocardial ischemia [5]. There was ongoing training for paramedics to conduct correct PH ECG electrode placement, but no assessment of clinicians' electrode placement who acquired the initial hospital ECG in the ED. Next, the presence of left ventricular hypertrophy (LVH) could not be reliably assessed on the PH ECGs in this investigation, since the validation study [4] did not assess diagnostic agreement for LVH. Lastly, this study sample provided insufficient power to detect a statistically significant difference in survival between patients with and with PH ECG ischemia. Therefore, the association between PH ECG ischemia and mortality remains inconclusive.

While limitations have been identified, it is important to note the following study strengths. Although patients were predominantly white and from two community hospitals (limiting generalizability), consecutive enrollment of patients with symptoms of ACS but a variety of final discharge diagnoses (ACS and non-ACS) was done 24 hours/day, 7 days week over 4 years, representing a “real life” EMS sample population. Next, vigorous data collection methods were used in the parent study (ST SMART) to obtain PH ECG data. Highly trained nurse researchers provided ongoing assessment and evaluation of paramedics who applied the ECG technology in the pre-hospital setting. Regular teaching sessions about the correct way to obtain ECG (i.e. skin preparation, lead placement) were conducted to ensure high quality ECG data were obtained. This vigor increases the validity of the PH ECG data utilized in this secondary analysis. Another study strength was the ability of the specialized ST-segment monitoring software to provide continuous detection of ischemic changes in all PH ECG leads. It is often difficult for the human eye to detect ST-segment changes since they may be subtle. Computerized ECG measurements are precise and eliminate human bias, which enhances the validity of the PH ECG data. An expert [JZH] interpreted the PH ECGs and initial hospital ECGs acquired for the study, and a second expert [CES] conducted random audits of ECG analyses (approximately 10%) to confirm the diagnosis of ACS and establish inter-rater reliability. These measures further enhance the validity of ECG data in this study. Finally, this was the first study to apply more recent universal ECG criteria for interpretation of PH ECG. Universal criteria were developed to increase the sensitivity and specificity of the ECG by recognizing gender and lead differences [6].

Clinical Implications

The results of this dissertation study underscore the importance of correctly identifying patients at risk for ACS early by the use of ECG technology in the pre-hospital setting. Using PH ECG data in conjunction with the initial ECG obtained on arrival to the ED significantly improves diagnostic methods to identify ACS. Considering these data together has implications for clinicians practicing in the ED setting since the correct identification of ACS patients remains a major challenge to clinicians. Serial ECG recordings (between PH ECG and initial hospital ECG) offer the opportunity for clinicians to observe changes between tracings that may be more difficult to interpret individually. In addition, serial ECGs may help detect evolving changes of ischemia that are by nature dynamic and unpredictable. The presence of PH ECG ischemia improves the ability to predict an ACS diagnosis, an important implication for risk stratification.

Clinical presentation of ACS may be unreliable since approximately 50% of patients with ACS report atypical symptoms [7]. Since patients presenting to the ED with ECG evidence of ischemia are at particular risk for adverse hospital outcomes, ST-segment monitoring used in the pre-hospital setting could enhance risk stratification for patients activating "911" for ACS symptoms. Successful risk stratification would identify patients both at high and low risk of being diagnosed with ACS and develop subsequent adverse events [7]. This strategy would facilitate more aggressive treatments faster for high-risk patients without subjecting low-risk patients to unnecessary treatment. Moreover, patients identified as high-risk could be considered for admission more promptly, and those identified as low-risk could be more appropriately treated in chest pain observation units. Based on findings from this study, integrating PH ECG data into triage and risk strategies in the ED may help optimize the early diagnosis and treatment of patients with ACS.

Future Directions

There are important opportunities for future research about PH ECG and cardiac systems of care. From a "clinical" perspective, future investigations are needed to examine important outcomes such as mortality in patients with PH ECG ischemia. To date, the association between PH ECG ischemia and long-term mortality remains inconclusive. Another question for future research is to determine who should receive PH ECG, since most of the prior research is geared towards patients with STEMI. For example, less is known about the role of PH ECG in the management of patients with unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI), which comprise the largest proportion of ACS cases. The present study evaluated all patients with and without ACS, but more information about UA and NSTEMI would be beneficial since little is known about the association between PH ECG and these specific entities of ACS, both more common than STEMI. Future research should address who should interpret PH ECG data. Diagnostic accuracy needs to be compared between computer algorithms, paramedics, and emergency physicians or cardiologists [8] to determine the most effective method for decision making. Finally, future studies about ST-segment monitoring PH ECG should be conducted in urban settings and with more diverse patients to enhance the generalizability of this study's findings.

From a "systems" perspective, future research needs to be aimed at identifying barriers to implementing successful PH ECG programs. Despite American Heart

Association recommendations and other consensus statements, the national use of PH ECG has been low and essentially unchanged from the mid-1990s. Lack of an effective system has resulted in less than 10% of patients with STEMI having received PH ECG [8]. Questions about effective hospital systems of care need to be addressed. Technology surrounding PH ECG may be part of the problem, and studies designed to examine specific issues such as transmission difficulties need to be done. Finally, since the cost of placing ECG equipment in ambulances is a known barrier [8], cost-effectiveness analyses are needed to determine the economic feasibility of PH ECG technology. It would be important to evaluate the cost-benefit ratio from different perspectives including that of patients, hospitals, payors, and the community at large. Future research about PH ECG in cardiac systems of care requires a multi-disciplinary approach that includes clinicians (physicians, nurses, paramedics), nurse scientists, engineers, economists, and policy makers.

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