Initial Clinical Results Using Intracardiac Electrogram Monitoring to Detect and Alert Patients During Coronary Plaque Rupture and Ischemia

Tim A. Fischell, MD, David R. Fischell, PhD, Alvaro Avezum, MD, M. Sasha John, PhD, David Holmes, MD, Malcolm Foster III, MD, Richard Kovach, MD, Paulo Medeiros, MD, Leopoldo Piegas, MD, Helio Guimaraes, MD, and C. Michael Gibson, MS, MD

From Borgess Heart Institute, Kalamazoo, MI (TAF), Mayo Clinic, Rochester, MN (DH), Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil (AA, PM, LP, HG), Rotman/IBBME, University of Toronto, Toronto, Canada (MSJ), AngelMed Systems, Inc., Shrewsbury, NJ (DRF, MSJ), Baptist Hospital West, Knoxville, TN (MF), Virtua Hospital, Cherry Hill, NJ (RK), and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (CMG)

Dr. Tim Fischell has received research grants, served as a consultant for, owns stock in, and has licensed patents to Angel Medical Systems. Dr. David Fischell is a co-investigator on a small business innovation research (SBIR) grant for developing a similar device that will use subcutaneous sensing of cardiac activity to detect ischemia. He is also the CEO and founder of, owns stock in, receives an annual salary from, and has licensed patents to, Angel Medical Systems. Dr. John is a co-investigator on a small business innovation research (SBIR) grant for developing a similar device that will use subcutaneous sensing of cardiac activity to detect ischemia. He also owns stock in Angel Medical Systems and receives an annual salary. Dr. Malcolm Foster has stock in Angel Medical Systems. Dr. Gibson has served as a consultant in the past (none in the past year) and received research grants from Angel medical Systems. None of the other authors has any relevant potential or actual conflicts of interest to report.

Short Title: Chronic Intracardiac Ischemia Detection (Characters =36)

Key words: vulnerable plaque, myocardial infarction, electrogram, ischemia monitoring.

Total words = 4600 (minus 57 in acknowledgments) =4543

Corresponding author:
C. Michael Gibson, M.S., M.D.
Chief Clinical Research, Beth Israel Deaconess Medical Center, Boston MA, 185 Pilgrim Road
Deaconess 319, Boston MA 0215
Email: mgibson@perfuse.org , Phone: 617-632-7754
ABSTRACT

Objective: We report the first clinical studies of intracardiac ST-segment monitoring in ambulatory humans to alert them to significant ST-segment shifts associated with thrombotic occlusion.

Background: Despite improvements in door-to-balloon times, delays in symptom-to-door times of 2-3 hours remain. Early alerting of the presence of acute myocardial infarction (MI) could prompt patients to seek immediate medical evaluation.

Methods: Intracardiac monitoring was performed in 37 patients at high risk for acute coronary syndromes. The implanted monitor continuously evaluated the patients’ ST-segments sensed from a conventional pacemaker RV apical lead, and alerted patients to detected ischemic events.

Results: During follow-up (median 1.52 years, range 126-974 days) 4 patients developed ST-segment changes of ≥ 3 standard deviations of their normal daily range, in the absence of an elevated heart-rate. This in combination with immediate hospital monitoring led to angiogram and/or IVUS which confirmed thrombotic coronary occlusion/ruptured plaque. The median alarm-to-door time was 19.5 minutes (6, 18, 21, and 60 minutes). Alerting for demand related ischemia, at elevated heart-rates, reflective of flow-limiting coronary obstructions, occurred in 4 patients. There were 2 false-positive ischemia alarms related to arrhythmias and 1 due to a programming error that did not prompt cardiac catheterization.

Conclusions: Shifts exceeding 3 standard deviations from a patient’s daily intracardiac ST-range may be a sensitive/specific marker for thrombotic coronary occlusion. Patient alerting was associated with a median alert-to-door time of 19.5 minutes in patients at high-risk of recurrent coronary syndromes who typically present with 2-3 hour delays.

(Words=244)
**Abbreviations:**

MI = myocardial infarction  
STEMI = ST-segment elevation myocardial infarction  
ICEG = intracardiac electrogram  
ECG = electrocardiogram  
BPM = heart rate in beats per minute  
IMD = implanted monitoring device  
EXD = the external device  
LAD = left anterior descending  
RCA = right coronary artery
Introduction.

Acute myocardial infarction (MI) remains a leading cause of mortality in the western world (1). Early detection of acute MI and prompt intervention may substantially improve clinical outcomes (2-7). Despite efforts to educate the public over the past decade, the mean time from MI symptom onset to arrival at a hospital for treatment has not changed, remaining at 2.5-3.0 hours (6-10). There may, in fact, be no reduction in pre-hospital delay between first and 2nd (or subsequent) heart attacks with a median of 2.4 hours for both first and second MI (12). Since a large proportion of irreversible myocardial injury and fatal ventricular arrhythmias occur in the first hours after coronary thrombosis, it may be difficult to further improve upon the prognosis of ST-segment elevation MI (STEMI) patients unless an earlier and reliable diagnosis can be made (6-14) that would in turn prompt patients to seek immediate care.

While fixed coronary artery narrowing may result in ST-segment depression with elevated heart rates (demand-related ischemia), rapidly progressive ST-segment shifts within the “normal” heart rate range (supply-related ischemia) is a highly specific, and early, marker of thrombotic (or vasospastic) coronary artery occlusion. Such ST-segment changes often precede, and may occur in the absence of, clinical symptoms. Continuous monitoring of a patient’s electrogram ST-segment may allow an implanted device to detect acute closure of a coronary artery. If the implanted device then alerted the patient, this could lead to a reduction in symptom-to-door time and thereby potentially improve clinical outcomes.

The current study reports the first in-human clinical experience with intracardiac ischemia monitoring, combining two, phase 1 studies including the CARDIOSAVER study
(conducted in Brazil) and the DETECT FDA investigational device exemption study (conducted in the US).

**Methods.**

**Subjects.**

Two phase 1 clinical studies CARDIOSAVER (N=20) and DETECT (N=17) assessed device safety and feasibility. Patient demographic data are summarized in Table 1.

**Ischemia Monitoring System Components.**

The AngelMed Guardian® implantable ischemia detection system (Angel Medical Systems, Shrewsbury, NJ) is designed to provide early detection and patient alerting for ischemic events in ambulatory patients. An implantable device monitors the intracardiac electrogram (ICEG) signal, acquired at 200 Hz using a band-pass of 0.25 Hz (2-pole) to 48 Hz (5-pole), from the tip of a steroid-eluting pacemaker-lead placed at the right ventricle apex. Using a can-to-tip vector, the implantable device monitors the ST-segment of the sensed ICEG to detect and alert patients to excessive ST-segment shift events. The algorithm computes the ST-segment shift of each beat compared to average baseline ST-segment levels sampled across the prior 24 hours and normalizes this as a percent of the baseline average R-wave height to derive a measure of ST-Shift%. Both positive and negative ischemia detection thresholds are defined for ST-Shift%. The implantable and external components of the system (see Figure 1) provide ischemia detection and alerting as has previously been described in detail (18, 24).
Study Protocol.

The CARDIOSAVER and DETECT protocols are described in Table 2. All patients participated only after reviewing and signing informed consent, as per Brazilian and U.S. (FDA) guidelines, and local approval from institutional review boards.

Patients returned within 2 weeks after surgical implantation to undergo a stress test used to program heart rate ranges and respective ischemia detection thresholds at levels that would not trigger an alert base upon the patient’s normal intrinsic ischemic burden. A “normal” heart-rate range was set for each patient by their physician, as was a maximum heart rate above which an alarm was defined. The range between normal and maximum was divided into 4 elevated heart rate ranges. The DETECT study utilized an automated threshold feature built into the programmer. The feature calculates ischemia detection thresholds using an initial period of up to two weeks of data and suggests positive/negative thresholds for different heart rate ranges. Thresholds are set for each heart rate range using a mean +/- a variance estimate. The variance was 3 standard deviations of measured ST-Levels compared to isoelectric (ST-Deviation) which occurred during this initial period (in the normal heart rate range). The CARDIOSAVER study initially set ischemia thresholds based upon clinical judgment but as the study progressed the automatically chosen thresholds were adopted.

Following device programming, patients underwent training to experience and distinguish between the two types of alarms (“Emergency” and “See Doctor”). Patients were then discharged. Patients were required to return:
• At 1, 3, and then 6 months follow-up intervals during which data were downloaded and reviewed to ensure proper monitor operation and to confirm that ischemia detection parameters did not require adjustment;

• If they had symptoms they thought were consistent with a cardiac problem, even if the device was not alerting; and,

• Due to an Emergency or See Doctor alarm according to the study protocols.

**Patient Alerting and Response Protocol.**

The Guardian system provides 2 types of patient alerting across 3 sensory modalities (Figure 1). Following detection of excessive ST-segment shift over 1.5 minutes, when the patient’s heart rate is not elevated, the system provides an Emergency alarm indicating thrombosis may be present. Patients were instructed to seek help immediately if an Emergency alarm occurred. For non-life threatening detections the monitor issued a “See Doctor” alarm. See Doctor alarms could be triggered by excessive ST-shift concurrent with an elevated heart rate, by the detection of additional conditions related to device operation, and by status-checks which the ischemia detection algorithm performed. All patients were trained to respond to See Doctor alarms by immediately calling their doctor to schedule an appointment within one to two days.
Data.

The results are from the CARDIOSAVER (active May, 2006-November, 2007) and DETECT (active June, 2007-current) studies, and include all study period data collected through January 1, 2009. The ICEG data were uploaded from implantable monitor’s memory during scheduled patient visits and visits made in response to alarms. The implantable monitor normally stores selected electrogram data strips from the preceding 24-hours. Following an Emergency alarm, strips for up to 8 hours after the alarm are also stored. Over 58 patient-years of aggregate monitoring produced more than 350,000 10-second electrogram strips which were uploaded into the study database.

Emergency Alarm Event Types.

Ischemic events were classified into three types. Type-1 events comprise alarms triggered by persistent excessive ST-shift% detected during, or following, an elevated heart-rate ("demand" related ischemia, typically seen in abnormal 12-lead exercise stress test data). Type-2 events comprise false-positive alarms which were unrelated to a verifiable ischemic condition. Type-3 events comprise alarms triggered by excessive ST-shifts detected at normal heart rates ("supply" related ischemia) without associated elevated heart rate consistent with coronary thrombosis.

Results

The 37 patients were monitored for a total of 58.2 patient/years (mean follow-up of 1.53±0.54 years, median follow-up of 1.52 years). The range of follow-up was from 126-974
days. The implant success rate was 37/37 (100%). One device replacement was required due to vibration alarm motor failure. No other device-related failures or complications occurred during the study period.

Five patients had Type-1 events, with positive ST-shift alarms at an elevated heart rate (2 patients), and negative ST-shifts at a non-elevated heart rate, following a period of elevated heart rate (3 patients). Three patients had Type-2 events, including false-positive ST-shift detections caused by an intermittent ventricular dysrhythmia, which required device reprogramming (2 patients) and a false positive occurring just after improper programming of the device thresholds before the patient left the hospital (1 patient). Four patients had Type-3 events which included excessive ST-shifts at “normal” heart rates, unrelated to any episode of elevated heart rate (see Figures 3-7).

Heart rate related ST-shift alarms (Type-1 events).

Figure 2A shows the plot of ST-Shift% versus heart rate (BPM) illustrating an example of a Type-1 event. As the heart rate elevates (red) there is ST-shift (depression). Figures 2B and 2C show the ICEGs at baseline (2B) and during demand ischemia (2C) related to an obstructive lesion of the right coronary artery revealed in that patient. The figure shows ST-shift levels remained depressed for up to 5 minutes after the patient’s heart rate recovered to normal levels. Three other patients had heart-rate related ST-shift alerts. These demand-related ST-shifts in the three other patients were all associated with hemodynamically significant new coronary obstructive lesions from either atherosclerotic progression or in-stent restenosis.
False positive ST-shift detections (Type-2 events).

Two false positive alarms occurred as the result of ventricular dysrhythmias. These caused the R-wave identification of the monitoring algorithm to measure the beats incorrectly, leading to a false Emergency alarm. The R-wave identification algorithm parameters were manually adjusted and no additional false positive alarms occurred in these two patients. A third false positive occurred due to a programming error.

Excessive ST-shifts at “normal” heart rates (Type-3 events).

Case studies are presented for seven “true positive” Emergency alarm events which occurred in four patients during the study period. Cases 1 and 2 are from the CARDIOSAVER study and 3 and 4 are from the DETECT study.

Case #1 – LCX Ruptured Plaque

The patient is a post-menopausal female with prior MI, diabetes, hypertension and hyperlipidemia who presented with unstable angina due to a 70% stenosis of the right coronary artery. The ischemia monitor was implanted during that hospitalization with RCA stenting one week later, as per protocol.

Six months later she presented one hour after an emergency alarm that occurred in the setting of chest pain lasting 10-20 minutes. Her troponin and 12-lead ECG were normal.

The ICEG data (Figure 3A-3D) demonstrated a 15-20 minute episode of significant positive ST-shift, which coincided with the alarm (12:20pm) and her symptoms, which
resolved by the time of hospital arrival. Treatment included intravenous unfractionated heparin and clopidogrel. Eleven hours after admission she had a recurrent episode of chest pain greater than that during the first event, and a second Emergency alarm occurred.

Of note, the simultaneous 12-lead surface ECG showed little change from baseline, and the troponin remained within normal limits. This second event prompted cardiac angiography which demonstrated a large increase in the severity of a lesion in the proximal portion of the left circumflex, compared to prior angiography (Figures 3E and 3F). IVUS confirmed the presence of a ruptured plaque. Four days after the second alarm, the patient underwent successful bypass surgery.

Case #2: - RCA Ruptured Plaque

The second patient is a 65-year-old male with hypertension and dyslipidemia who presented with new onset angina (CCAS II) due to a 70% mid LAD lesion, associated with a positive exercise test (2-3 mm ST depression at peak exercise). The patient underwent elective stent placement in the LAD one week following device implantation.

Eighteen months later the Emergency alarm was triggered, while he was picking up medication at the hospital, due to a significant positive ST-shift% (~65%), which persisted at > 30% for more than 30 minutes and was accompanied by minimal symptoms.

The patient was admitted, aspirin and intravenous unfractionated heparin were administered. Nine hours later a second Emergency alarm occurred due to recurrent ST elevation (peak ST-Shift exceeding 35%) which resolved over the next 2 hours (Figure 4, top panel) in the absence of symptoms. The patient underwent angiography the following
morning (Figure 4C) which demonstrated a severe, eccentric lesion with a ruptured plaque (Figure 4D and 4E) in the distal portion of a dominant right coronary artery.

Case #3: LAD Ruptured Plaque

This is a 65-year old male with renal insufficiency, hypertension, dyslipidemia, and an MI eight years prior to enrollment. Approximately one-month prior to study enrollment and implantation he presented with unstable angina (CCSA IV). Approximately one month after implantation, he had an Emergency alarm triggered by an ST-shift of -24% (Figures 5A-C, -18% was detection threshold) while watching the Super Bowl. The surface 12-lead ECG in the ER was inconclusive, but troponin I levels were elevated and a nuclear stress test detected anterior ischemia. Angiography revealed a 70% stenosis in the mid portion of the LAD which was treated with primary stenting.

A second emergency alarm was triggered 3 weeks later by a negative 24% ST-shift at a normal heart rate (Figures 5D-F). The subject was immediately transported to the hospital. The 12-lead surface ECGs and cardiac enzymes were inconclusive. Angiography demonstrated a 70% stenosis in the LAD distal to the (patent) first stent. IVUS confirmed that this distal lesion contained a ruptured plaque. The patient was treated with a coronary stent, with the possibility that the distal lesion, and not the originally stented lesion, may have been the “culprit” lesion that triggered both ischemic events. Since stenting of the second lesion the patient has had no recurrent ischemic events.
Case #4: STEMI.

This patient is 60-year old white female with coronary artery disease, hypertension, dyslipidemia, and a long history of smoking. Nine months after implantation the patient developed severe chest pain. Nineteen minutes after the onset of her chest discomfort she received an emergency alarm. A 12-lead ECG performed by paramedics in the ambulance was mildly abnormal with ST-segment abnormalities in the inferior leads and clear T-wave changes in the precordial leads (Figure 6A).

The 12-lead ECG in the emergency room demonstrated ST depression in the anterior precordium consistent with a posterior MI as shown in Figure 6B The Emergency alarm was triggered by a positive 17% ST-shift (11% was ischemia threshold) at a normal heart rate. The ST-shift%/heart rate plot and the ICEG tracings are shown in Figures 7A-C. The total creatinine kinase (CK) and troponin were elevated shortly after arrival at the hospital. The subject was taken emergently for coronary angiography. A new subtotal occlusion of the proximal left circumflex was found (Figures 7D and 7E). She was stented (Figure 7F), and was discharged without complications or further alarms.

Behavioral results.

Each of the four case study patients responded quickly to the Emergency alarm, regardless of concurrent subjective symptoms. Cases 1, 2, 3, and 4 had alarm-to-door times of 60, 6, 18, and 21 minutes, respectively (mean 26.5 min./median 19.5 min.).
Discussion

This study demonstrates the safety and feasibility of ICEG monitoring to detect and alert patients to ischemic events associated with documented plaque rupture and/or thrombotic occlusion ("supply" related ischemia at normal heart rate). Alarms also occurred at elevated heart rates in response to disease progression in fixed obstructive lesions such as is observed during abnormal (12-lead) stress test ("demand" related ischemia). The discrete shifts in the ST-segment that triggered Emergency alarms were large and exceeded the small day-to-day variation in ST-shifts (less than ±10% in the normal heart rate range) by three standard deviations for at least 1.5 minutes.

Four patients had seven ST-shift detections in the setting of a normal heart rate triggering Emergency alarms associated with STEMI, a severe coronary lesion, and/or with IVUS evidence of plaque rupture. The mean alarm-to-door of 26.5 min. (median 19.5 min.), is approximately two hours faster than the 144 minute symptom-to-door time observed in general STEMI patient populations (12). Seeking medical care two hours earlier, during the beginning of acute MI, may be associated with significant improvements in clinical outcomes including reductions in the development of heart failure and mortality.

Several potential explanations exist for the observation that some Emergency alarms occurred in the absence of troponin elevation, surface ECG changes and/or symptoms (e.g., Case #3) although plaque rupture or thrombus was documented on intravascular ultrasound. The ICEG may be more sensitive than 12-lead surface ECGs, particularly for detection of injury involving the posterior aspect of the left ventricle. Indeed, in Case Studies 1 and 4 the surface
12-lead ECG was insensitive to left circumflex coronary artery occlusion. This finding is consistent with prior demonstrations that the ICEG is more sensitive than surface ECG to balloon occlusion during angioplasty (13-16). Further, the real-time quantification available from a self-normative implanted monitor increases sensitivity compared to traditional ECG. In some patients, the ICEG recordings may have reflected transient coronary occlusion and/or cyclic flow variations in the early period after plaque rupture and before formation of a stable occlusive clot (19-23).

Patients may not sense chest pain, despite ischemia, possibly as a result of a defective anginal warning system. For example, in the Framingham experience, 1 in 4 new q-wave MIs were silent (25). Given the mild nature of symptoms, some patients (e.g. Case 2) may not have sought medical attention in the absence of device alarming. Intracardiac electrogram data may not only prompt the patient to seek medical attention earlier, but being more sensitive than the surface ECG, a more definitive pre-hospital diagnosis may further reduce door-to-balloon times by improving triage decisions in the emergency room.

Three false positive events comprise the only false positive alarms during 58 patient-years of monitoring. These false positive detections, which appear to be secondary arrhythmias, permitted early adjustments in the monitoring algorithm. After these adjustments, no additional false positives occurred. No false negative alarms occurred during the study period: there were no undetected STEMI, cardiac deaths or Q-wave MIs in any of the cohort during the follow-up. No clinically significant unanticipated adverse device-related
events occurred in any patient. The monitor’s safety profile is anticipated to be similar to the safety of a single chamber pacemaker.

Limitations.

The number of Emergency alarms reported here is consistent with the 5% to 10% risk of acute MI in this population. The number of cases here is too small to evaluate the clinical impact of early detection of ST-shifts. In this study Emergency alarms were not intended to trigger immediate trips to the catheterization laboratory. However, Emergency alerting was subsequently associated with thrombotic occlusion or ruptured plaque. None of the false positive cases underwent cardiac catheterization. Whether patients should proceed to the cardiac catheterization laboratory earlier is not addressed in the present study. These issues are now being addressed in a Phase II randomized clinical trial (ALERTS) of 1,000 patients. It is possible that “silent” ischemic events occurred which did not cause Emergency alarms and for which the patient did not experience symptoms and seek hospitalization. In the ALERTS trial, the development of new Q-waves in the absence of symptoms will be evaluated. Early alerting and treatment of patients in the early phase of an acute coronary syndrome may minimize or prevent the progression to a higher-risk, more established ACS or acute MI. Paradoxically, this scenario may obscure the ability to demonstrate that MIs were detected early if they were in fact prevented. This issue will be addressed by the control group in the ALERTS trial. There were no control patients in the present study, and the expected rate of
resource consumption will be addressed by the control group in the ongoing randomized ALERTS trial who will not receive Emergency alarms.

**Conclusions.**

This study represents 58.2 patient-years of monitoring and more than 18 million monitored electrogram segments in a population at high risk for recurrent thrombotic events. Long term intracardiac ST-deviation appears relatively stable in the absence of substantial coronary artery occlusions. A shift of 3 standard deviations from a patient's normal daily ST-range on ambulatory intracardiac monitoring may be a sensitive/specific marker for plaque rupture and/or thrombotic coronary occlusion. Early warning was associated with a median alert-to-door time of 19.5 minutes in patients at high risk of recurrent coronary syndromes who typically present with delays of 2-3 hours.
Acknowledgments:

We would like to acknowledge the substantial contributions of Jill Schweiger, Steven R. Johnson, Jonathan P. Harwood, David Keenan, Richard Bantel, Bruce Hopenfeld, Dan Keenan, Nick Nudell, Rob Granger, David France, Maggie MacKenzie, Denise Boyd, Shannon Welsh, Rosana Nakamura, and Santiago Marques to this paper. We would like to recognize Angel Medical Systems, Inc. for study funding. (Words=57)
Figure Legends.

Figure 1. Guardian System. Panel A shows a schematic of the components of the ischemia detection system. The implanted monitoring device (IMD) communicates with the external device (EXD) via telemetry. The EXD can be connected to the programmer by a cable in order to provide programming and data uploading from the IMD. Panel B shows photographs of the Guardian components. The monitor (C), resembling a VVI pacemaker, is attached to the lead adapter (D) and a standard bipolar, active-fixation, right ventricular lead (E). The implanted device emits distinct patterns of vibratory alarms and the EXD (F) provides sonic and visual notification with a red/yellow light for Emergency/See Doctor alarms. Two highly distinguishable patterns, which conform to international medical equipment alarm standards, differentiated the two types of patient alarms. The patient halts alerting by placing the EXD on their chest and pressing the EXD’s “alarm silence” button.

Figure 2. Heart rate related ST-Shift% alarms. The top panel shows heart rate (BPM; red) vs. ST-Shift% (blue) over time. Time is represented in minutes across a period of about 20 hours (log scale). Time zero is when the alarm occurred. The lower two plots are electrogram strips from the patient’s baseline (B) and at the time of the alarm (C) showing substantial ST-depression.
Figure 3. Case #1. Panel A shows heart rate (BPM; red) vs. ST-Shift% (blue) over time. Pink lines denote ST-shifts that triggered the two Emergency alarms. The baseline intracardiac electrogram tracings from the day before the alarm are shown in panel B. Panel C shows ICEG tracings at ~12:20, during the first emergency alarm, demonstrating significant T-wave peaking and ST-elevation compared to baseline. Peak ST-shift% was 39%, at normal heart rate, with threshold set at +/-25%. Panel D demonstrates the rapid, beat-to-beat elevation of ST-segment and T-wave peaking during the second emergency alarm (ST-shift%=30%). The shaded boxes highlight the rapid evolution of the ST-Shift from a waveform similar to panel B (blue shadowing) to substantial ST changes (pink shadowing) over a series of 7-10 beats. Panel E shows the baseline angiogram of the left circumflex lesion (yellow arrow). Panel F shows the pronounced progression of the proximal left circumflex lesion at the time of admission for recurrent ischemic alarm events. IVUS demonstrated a ruptured plaque at the site of the red arrow.

Figure 4. Case #2. The top panel shows heart rate (BPM; red line) vs. ST-Shift% (blue line) over time. Two emergency alarms occurred as denoted with pink lines. Panel B shows the baseline angiogram of the right coronary artery (May, 2006) and the subsequent angiographic findings at the time of emergency alarming (C; November, 2007). Lesion progression, with IVUS evidence of plaque rupture (Panels D and E), is evident. Dashed and solid lines denote the location of IVUS sections shown in C and D. Arrows denote site of plaque rupture.
Figure 5. **Case #3: ICEG Data.** Panel A shows the plot of heart rate versus ST-shift% over time with pink line denoting the shift during the Emergency alarm. Panels B (baseline) and C (Emergency alarm) show emergence of ST-depression in the ICEG data, typical for left anterior descending occlusion. Panels D, E and F show similar results from the patient’s second Emergency alarm.

Figure 6. **Case #4: Surface 12-lead ECGs.** Panel A shows the 12-lead ECG at ambulance arrival (7 AM). Panel B shows the evolution to “true posterior” ST elevation MI (circled beat in lead V2) at 7:20 AM, during hospital arrival.

Figure 7. **Case #4: ICEG data and angiographic findings.** Panel A plots heart rate versus ST-shift% over time with pink line denoting the change that prompted the Emergency alarm. Panel B shows the baseline ICEG. Panel C shows the ST-segment elevation that triggered the emergency alarm. ST-segment elevation persisted until successful stenting of the sub-totally occluded left circumflex (see Figure 10). Of note, the alarming ST-shift in the ICEG was evident more than 30 minutes before 12-lead ECG findings were diagnostic for STEMI (Figure 6B). Panels D and E show a prior angiogram of the left circumflex coronary artery (October, 2007) and at the time of Emergency alarm (July, 2008), respectively. Marked lesion progression to sub-total occlusion is evident at follow-up (white arrow). Panel F shows the result after stent placement.
References.


22.  Vetrovec, G. W. Improving Reperfusion in Patients with Myocardial Infarction. NEJM 2008; 358: 634-637


Fischell et al. Figure 5

Graph A: BPM vs. Time since Emergency Alarm (minutes)
- ST Shift (% of R-wave height)
- Heart Rate
- Emergency Alarm

Graph B & C: ECG tracings with different heart rates.

Graph D: BPM vs. Time since Emergency Alarm (minutes)
- ST Shift (% of R-wave height)
- Heart Rate
- Emergency Alarm

Graph E & F: ECG tracings with different heart rates.
A

B

Fischell et al. Figure 6
Table 1. Demographic Data.

<table>
<thead>
<tr>
<th></th>
<th>CARDIOSAVER</th>
<th>DETECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (Yrs)</td>
<td>60 (49-70)</td>
<td>60 (42-71)</td>
</tr>
<tr>
<td>Female gender</td>
<td>3/20 (15%)</td>
<td>5/17 (29%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>13/20 (65%)</td>
<td>11/17 (65%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5/20 (25%)</td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9/20 (45%)</td>
<td>13/17 (76%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STEMI 7 (41%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSTEMI 6 (35%)</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>5/20 (25%)</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>Mean coronary diameter stenosis</td>
<td>71.4%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 2. Protocols for CARDIOSAVER and DETECT Phase I Studies.

<table>
<thead>
<tr>
<th>CARDIOSAVER Study (Sao Paulo, Brazil)</th>
<th>DETECT Study (U.S.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location Patients Recruited and Implanted</strong></td>
<td><strong>Location Patients Recruited/Implanted</strong></td>
</tr>
<tr>
<td>Dante Pazzanese Institute of Cardiology, Sao Paulo, Brazil</td>
<td>Borgess Heart Institute, Kalamazoo, MI Virtua Hospital, Marlton, NJ Baptist Hospital West, Knoxville, TN</td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td><strong>Primary objective</strong></td>
</tr>
<tr>
<td>To evaluate the ability of the Guardian ischemia detection system to measure intracardiac ST segment shifts associated with subendocardial ischemia during a stress test and transmural ischemia during 3-minute coronary occlusion in PCI (balloon and stent placement).</td>
<td>To evaluate the safety of the Guardian ischemia detection system and to evaluate algorithm for suggesting appropriate ST shift detection thresholds</td>
</tr>
<tr>
<td><strong>Study population - 20 Enrolled, 20 Implanted</strong></td>
<td><strong>Study population - 20 Enrolled, 17 Implanted</strong></td>
</tr>
<tr>
<td>- CAD patients, stable angina (CCS)</td>
<td>- Post MI patients with other risk factors</td>
</tr>
<tr>
<td>- Age ≥ 40 yrs and &lt;70 yrs</td>
<td>- TIMI 3 flow or worse</td>
</tr>
<tr>
<td>- &gt;1.5mm ST depression on a stress test</td>
<td>- Implant suitability</td>
</tr>
<tr>
<td>- Stenosis in native coronaries, PCI indicated</td>
<td><strong>Procedures</strong></td>
</tr>
<tr>
<td>- Implant suitability</td>
<td>1. System implant (pacemaker lead in the RV)</td>
</tr>
<tr>
<td><strong>Procedures</strong></td>
<td>2. Wait 5-10 days until ST back to baseline</td>
</tr>
<tr>
<td>1. System implant (pacemaker lead in the RV)</td>
<td>3. Stress test to get data at elevated heart rates</td>
</tr>
<tr>
<td>2. Stress test (pre- PCI)</td>
<td>4. Device programming using automatic and statistically-based thresholds</td>
</tr>
<tr>
<td>3. PCI after ST returned to baseline (5-10 days)</td>
<td>5. Patient training on the alarm recognition</td>
</tr>
<tr>
<td>4. Balloon inflation for 3 min</td>
<td>6. Discharge and follow-up</td>
</tr>
</tbody>
</table>
| 5. Standard stent placement | **Key:**  
PCI = percutaneous coronary intervention  
RV = right ventricle  
TIMI = thrombolysis in myocardial infarction  
| 6. Patient training on the alarms recognition | CAD = coronary artery disease  
MI = myocardial Infarction  
CCS = Canadian cardiovascular society |
| 7. Discharge and follow-up |  