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Original article

The prediction of the in-hospital mortality of acutely ill medical patients by electrocardiogram (ECG) dispersion mapping compared with established risk factors and predictive scores — A pilot study

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ABSTRACT

Objective: ECG dispersion mapping (ECG-DM) is a novel technique that analyzes low amplitude ECG oscillations and reports them as the myocardial micro-alternation index (MMI). This study compared the ability of ECG-DM to predict in-hospital mortality with traditional risk factors such as age, vital signs and co-morbid diagnoses, as well as three predictive scores: the Simple Clinical Score (SCS) – based on clinical and ECG findings, and two Medical Admission Risk System scores – one based on vital signs and laboratory data (MARS), and one only on laboratory data (LD).
Methods: A convenient sample of 455 acutely ill medical patients (mean age 69.7 ± 14.0 years) had their vital signs, mental and functional status recorded and a 12 lead ECG, routine laboratory investigations and ECG-DM performed immediately after admission to hospital. Each patient's in-hospital course and diagnoses at death or discharge were reviewed.
Results: Of the vital signs only oxygen saturation and respiratory rate were statistically significant predictors of death. The continuous variables that predicted death the best were: MARS, SCS, LD, white cell count and MMI. The categorical variables that predicted in-hospital mortality with highest Chi-square were: a diagnosis of stroke, SCS >= 12, LD>0.10, MARS >0.09 and MMI >36%.
Conclusion: ECG-DM may be a clinically useful predictor of in-hospital mortality. ECG-DM is inexpensive, only takes a few seconds to perform and requires no skill to interpret.

1. Introduction

The majority of inpatient workload in hospitals is now generated by emergency admissions and there is a wide variation in the mortality rates, length of stay and possibly standards of care between different units [1]. Currently there is no consensus as to what conditions or complaints require hospital admission. It used to be that this decision was left to the patient's doctor, but as competition for beds has become keener most hospitals now assess the need for admission in their accident and emergency department. Unfortunately there are no explicit assessment processes, and often very sick patients are kept on a trolley awaiting laboratory tests results or, ironically, a doctor experienced enough to recognize the seriousness of their condition. Explicit accurate estimation of the severity of illness and risk of death would help ensure that an appropriate level of care is promptly provided to all patients.

There are many factors associated with increased mortality among medical patients admitted to hospital as emergencies which have been incorporated into risk-stratification clinical scoring systems. The Simple Clinical Score (SCS) can, at the time of admission, accurately predict the risk of death within 30 days [2]. This score can be quickly performed at the bedside and requires no additional information or investigation other than a 12 lead ECG, and accurately places patients into one of five risk groups. The SCS identifies severity of illness, functional status and co-morbid conditions — the three factors recognized as the major determinants of mortality [3]. We have also recently reported the Medical Admission Risk System score (MARS) — a multivariable fractional polynomial logistic regression model using only vital signs and elementary laboratory work that accurately predicts the in-hospital mortality of unselected acute medical patients [4]. MARS had excellent calibration and discrimination on internal validation and also on external validation in a small rural hospital. Very little of the score's discrimination was sacrificed by only using its laboratory components (the LD score). Both scores, however, require the expense and delay of laboratory testing.

Ideally prediction rules should be easy, quick and cheap to use and predict something important and clinically relevant. They should also provide accurate predictions over as wide a range of clinical situations as possible [5]. The SCS was derived from 6736 unselected acute medical admissions to our hospital and validated in 3228 patients and

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has an AUROC over 90% for the prediction of death within 24 h of admission. Independent external validation has confirmed that it has an area under the receiver operator characteristic curve (AUROC) of 85% for the prediction of in-hospital mortality [6,7]. It is, therefore, more discriminative than any of the other early warning scores based on clinical findings currently available [8].

The four most important components of the SCS are hypotension, hypoxia, hypothermia, inability to stand unaided and ECG abnormality — only four out of 4177 patients with a normal ECG died within 24 h [9]. ECG changes are, therefore, an important component of the SCS. However, performing and interpreting an ECG is time consuming, requires training and skill and can, therefore, be costly and impractical. ECG dispersion mapping (ECG-DM) is a recently developed technology that may provide non-invasive assessment of myocardial pathology by analyzing low amplitude oscillations of conventional ECG signals. This method examines not only the tiny fluctuations of the T-wave (T wave alternans) but also micro fluctuations of the P wave and QRS complex. All these micro-deviations are combined into one overall myocardial micro-alternation index (MMI) which is expressed as a percentage [10–12] — if pathological micro-deviations are present throughout the entire myocardium the MMI is 100%, whereas an MMI of 0% indicates a total absence of abnormal micro-deviations. The MMI reflects abnormalities in the myocardium at a metabolic level, which may include ischemia and other causes. An ECG-DM, therefore, is not diagnostic but a non-specific indicator of myocardial health. Measurement is carried out not only directly on an ECG-signal but also indirectly by examining the asymmetry of the ECG signal between the right and left ventricles, which allows signal averaging to be obtained within 30 s. From the six traditional ECG leads of I, II, III, aVR, aVL and aVF patented formulae can determine asymmetry of the ECG signal between the ventricles in a very short time [11]. This signal is highly accurate and correlates with the amplitude of micro-alternations not only of the T wave but of the entire PQRS complex. This method is much more sensitive than direct "beat to beat" measurement of ECG micro-alternations, and this allows measurements to be performed at rest. ECG-DM only takes a few seconds to perform and requires no skill to interpret and was primarily developed as a rapid screening test for heart disease. The role of this new technology in clinical medicine is still being defined. This study compared the ability of ECG-DM to predict in-hospital mortality with the traditional risk factors such as age, vital signs and co-morbid diagnoses, as well as the SCS, MARS and LD scores.

2. Methods

All patients were recruited from the unselected acutely ill medical patients admitted to Nenagh Hospital between July 30th 2009 and 31st March 2010. Of the 1680 patients admitted during this period 455 (27.1%) were included in the study — the only criterion for study inclusion was that one of the authors was able to perform an ECG-DM on them within 10 to 20 min of hospital admission. ECG-DM (HeartVue System, Medical Computer Systems Ltd., Moscow) is a non-invasive procedure that takes 30 s to perform, and only requires the placement of the four standard ECG limb leads. Patients studied had the same age (68.0 ± 16.7 vs. 66.1 ± 19.0 years, $p = 0.053$), length of hospital stay (6.7 ± 7.0 vs. 7.2 ± 7.9 days, $p = 0.24$) and in-hospital mortality (3.5% vs. 3.6%, $p = 0.94$) as the other patients admitted during the study period.

Nenagh Hospital is a small general hospital in rural Ireland serving a population of 60,000. It has a 36 bed acute medical unit with 2800 admissions per year almost all of which are unplanned emergencies [13]. It is served by four consultant physicians each assisted by a team of three physicians in training — each team is on-call every fourth day. The hospital has a five bed ICU capable of cardiac monitoring, external and temporary transvenous pacing, non-invasive and invasive ventilations etc. Renal dialysis, hematology and oncology units are available at Limerick Regional Hospital, 25 miles away. The overall in-hospital mortality rate for acute medical patients is 3.7% and not significantly different from the rate of 3.3% reported by the Limerick Regional Hospital, the nearest teaching hospital and tertiary referral center.

Several categorical variables are well known to predictors of in-hospital mortality: a blood pressure below 100 mm Hg, a pulse rate greater than systolic blood pressure, hypo or hyperthermia, a respiratory rate over 20 breaths per minute, and oxygen saturation below 95%. In addition an abnormal ECG, breathlessness, prior illness (requiring some part of the daytime to be spent in bed), inability to stand without help, nursing home residence, and a new stroke are powerful predictors of mortality and included in the SCS [2]. The ability of all these categorical variables to predict mortality in our patient cohort was explored. We also examined the ten commonest of 32 co-morbid diagnoses that we have previously reported to have an increased risk of in-hospital mortality (i.e. heart failure, atrial fibrillation, diabetes, hyponatremia, chronic obstructive lung disease, anemia, altered mental status, pneumonia, neoplasia and acute myocardial infarction) [13].

The continuous variables of age, MMI etc. were converted into categorical variables by determining the threshold levels with the highest odds ratio for predicting in-hospital mortality. This was done by a process of trial and error. Continuous variables were compared by Student's *t* test and categorical variables by Chi-square — all calculations were performed using *Epi-Info version 6.0* (*Center for Disease Control and Prevention, USA*), and statistical significance was set at a p value of <0.05.

Ethical approval of the study was obtained from the *Mid-Western Regional Hospital Complex Scientific Research Ethics Committee*, which granted exemption for patient consent.

3. Results

Of the 455 patients studied 16 died during their hospital admission — 75% were women and only one patient who died was under 68 years of age. Of the traditional vital signs only oxygen saturation and respiratory rate were statistically significant predictors of death. All of the routine laboratory investigations except potassium levels were statistically associated with mortality. All three predictive scores were

Table 1
In-hospital mortality associated with different continuous variables. MARS — Medical Admission Risk System (see Reference [4]).

	Alive (n 439)	Dead (n 16)	F statistic	P
Age in years	67.7 ± 16.8	77.5 ± 9.0	5.401	0.02
Systolic blood pressure (mm Hg)	142 ± 26	133 ± 22	1.90	0.17
Diastolic blood pressure (mm Hg)	79 ± 16	74 ± 15	1.61	0.21
Mean arterial pressure (mm Hg)	99 ± 18	93 ± 17	1.846	0.17
Pulse rate per minute	84 ± 21	95 ± 21	3.463	0.06
Temperature (°C)	36.6 ± 0.7	36.6 ± 0.6	0.099	0.75
Oxygen saturation (%)	95.5 ± 3.6	92.7 ± 6.9	8.633	0.0035
Breathing rate per minute	20.7 ± 4.6	23.5 ± 7.4	5.445	0.02
Hemoglobin (g%)	13.0 ± 2.2	11.8 ± 1.6	4.867	0.028
White blood cell count (10^9/L)	10.4 ± 4.7	15.6 ± 9.2	17.341	0.00004
Serum sodium (mmol/L)	139 ± 5	136 ± 6	4.676	0.03
Serum potassium (mmol/L)	4.4 ± 0.6	4.3 ± 0.6	0.066	0.80
Urea (mmol/L)	8.9 ± 7.9	12.9 ± 10.0	3.876	0.05
Simple Clinical Score	6.3 ± 3.8	11.1 ± 3.6	23.70	0.000002
MARS score	0.109 ± 0.183	0.354 ± 0.298	24.544	0.000001
Laboratory Data (LD) Score	0.124 ± 0.164	0.336 ± 0.300	22.279	0.000003
Myocardial micro-alternation index (%)	23.1 ± 13.5	34.3 ± 17.2	10.440	0.001

Table 2
Odds ratio for in-hospital mortality associated with different categorical variables. The diagnoses tested are the ten commonest diagnoses associated with in-hospital mortality admitted to Nenagh Hospital (see Reference [8]).

	Odds ratio for in-hospital mortality (95%CI)	Chi-square	P
Age >68 years	11.55 (*1.57–240.59*)	8.79	0.003
Female sex	3.82 (*1.11–14.44*)	6.01	0.01
Vital signs			
Systolic blood pressure <100 mm Hg	2.47 (*0.00–12.59*)	1.42	0.23
Pulse rate > systolic blood pressure	4.17 (*0.86–17.53*)	5.23	0.022
Temperature <35 °C or >=39 °C	0.00 (*0.00–47.03*)	0.15	0.70
Respiratory rate > 20/min	2.48 (*0.82–7.62*)	3.31	0.07
Oxygen saturation <95%	4.92 (*1.61–15.26*)	11.36	0.0008
Other Simple Clinical Score variables			
Abnormal ECG	5.97 (*0.81–124.57*)	3.81	0.051
Breathlessness	1.90 (*0.63–5.75*)	1.63	0.20
Prior illness — some part of daytime in bed	5.95 (*1.93–18.40*)	14.84	0.0001
Unable to stand unaided	3.65 (*1.17–11.21*)	7.01	0.008
Nursing home resident	4.39 (*1.11–16.06*)	7.0	0.008
Diabetes	1.95 (*0.51–6.87*)	1.32	0.25
Stroke	17.96 (*3.83–80.74*)	32.3	0.00000001
Atrial fibrillation	0.78 (*0.12–3.75*)	0.11	0.75
Diagnoses associated with mortality			
Heart failure	3.29 (*1.06–10.07*)	5.85	0.02
Sodium <134 mmol/L	2.85 (*0.73–10.17*)	3.33	0.07
Chronic obstructive lung disease	0.36 (*0.02–2.68*)	1.06	0.30
Hemoglobin <11 g%	1.76 (*0.38–6.99*)	0.75	0.39
Altered mental status	2.54 (*0.65–9.01*)	2.6	0.11
Pneumonia	2.07 (*0.54–7.28*)	1.55	0.21
Cancer	3.78 (*0.00–20.07*)	3.19	0.07
Acute myocardial infarction	6.10 (*1.23–26.72*)	8.80	0.003
Myocardial micro-alternation index >38%	5.97 (*1.93–18.45*)	14.90	0.0001
Predictive scores			
Laboratory Data (LD) Score > 0.10	9.97 (*2.57–45.33*)	18.39	0.00002
Simple Clinical Score >=12	11.54 (*3.63–36.85*)	31.86	0.00000002
MARS score >0.09	7.00 (*2.16–23.94*)	16.33	0.00005

highly significant predictors of mortality. The continuous variables that predicted death with the highest F-statistic and lowest P values were: white cell count, MMI and the MARS, SCS and LD scores (Table 1).

The majority of the patients with a normal ECG (87%) had an MMI below 20%. Fifteen of the 16 patients who died had an abnormal ECG (odds ratio of 5.97) — this finding just failed to reach statistical significance (Chi-Square 3.81, p 0.051). All deaths occurred between 2 and 29 days after admission. Five of the 271 patients (1.8%) with a MMI below 20% died — all but one died 10 or more days after admission, four had a SCS on admission of >=10, two patients died from stroke, one from respiratory infection and one from pulmonary fibrosis (Table 2). The one patient who died from a myocardial infarction with a "normal" MMI was 87 years old and admitted with an acute intestinal obstruction that was managed conservatively. At the time of admission her ECG was normal. Eleven days later she suffered ECG changes of acute myocardial infarction and died before her troponin levels became elevated. Of the remaining 184 patients with MMI greater than 20% eleven (6.0%) died (Fig. 1).

The categorical variables that predicted in-hospital mortality with highest Chi-square number were: a diagnosis of stroke, SCS >=12, LD > 0.1, MARS > 0.09 and MMI > 36% — eight of the 71 (11.3%) patients with an MMI > 36% died (odds ratio 5.97, Chi-square 14.9, p < 0.0001). The diagnosis of stroke was the most powerful predictor of death (Chi-square 32.3), closely followed by a SCS >=12 (Chi-square 31.86). The only other diagnoses associated with in-hospital mortality were heart failure and acute myocardial infarction. Of the categorical variables based on vital signs only a pulse rate greater than the systolic blood pressure and oxygen saturation below 95% predicted mortality (Table 3).

4. Discussion

This small study of a convenient sample of patients is obviously limited. The patients studied represent those patients we were able to see very promptly after their arrival in our hospital. Since the authors worked a one-in-four 24 hour roster and 27% of admissions were studied the patients represent most of the patients the authors cared

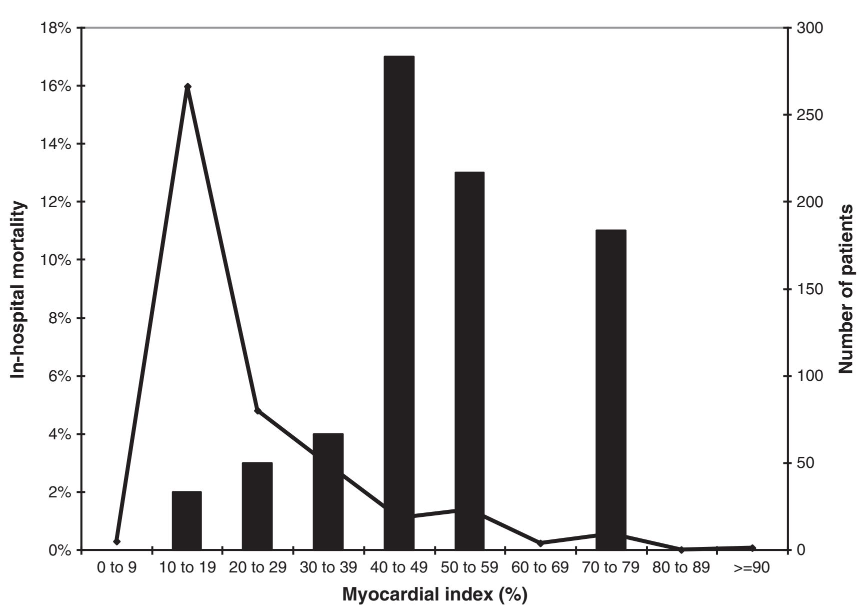

Fig. 1. In-hospital mortality associated with increasing levels of the myocardial micro-alternation index (MMI).

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Table 3
Cause of death of 16 patients that died MMI = myocardial micro-alternation index.

	Diagnosis	Age (years)	MMI	Days in hospital to death
1	Cardiac arrest	78	71%	2
2	Ruptured aortic aneurysm	88	53%	2
3	Myocardial infarction and CHF	83	38%	29
4	Myocardial infarction and CHF	70	50%	2
5	Myocardial infarction/intestinal obstruction	87	14%	11
6	Heart failure	75	44%	7
7	Stroke	88	28%	11
8	Stroke	72	19%	10
9	Stroke	58	15%	24
10	Pneumonia	69	40%	11
11	Pneumonia	72	35%	6
12	Pneumonia	90	25%	11
13	Pneumonia	75	14%	17
14	Sepsis	83	41%	13
15	COPD	83	50%	8
16	Pulmonary fibrosis	69	12%	3

for. As far as we are aware this is the first study to explore the prognostic capacity of ECG-DM and compare it with other predictors of in-hospital mortality. Our findings suggest that ECG-DM is a significant predictor of in-hospital mortality comparable to hypoxia and an elevated white cell count.

It is important to stress that ECG-DM should not be relied upon for diagnostic purposes. Of 19 patients who had acute myocardial infarctions six had normal MMI values (i.e. <20%) early in their presentation — two of these patients had obvious classical acute ischemic changes on 12 lead ECG at the time ECG-DM was performed. This disappointing result suggests that ECG-DM may only detect "damaged" myocardium, and that early in the presentation of acute infarction sufficient damage had not yet occurred. It is important to stress that none of these patients died. Moreover, the correlation between traditional ECG changes – especially transient ones that occur during acute infarction – and the extent of myocardial damage is also poor. ECG criteria alone are not sufficient to define myocardial infarction, the final diagnosis depending on the detection of elevated levels of cardiac biomarkers [14].

The small size of this study makes it likely that several of its findings may result from chance. For example the well established increased risk of hypotension [15] was not demonstrated and the finding that female sex is an independent predictor of in-hospital mortality is most likely explained by chance. In order to allow for this the p value could have been set by the Bonferroni method [16] at a very low level of 0.05 divided by 27, the number of categorical variables examined (i.e. 0.05/27 = 0.002). If this had been done then only oxygen saturation, prior illness, stroke, MMI and the SCS, LD and MARS scores would have remained as significant predictors of mortality.

The use of logistic regression to determine if the variables we tested were independent predictors of mortality is problematic because of the small number of deaths we observed. Ideally there should be 10–20 events per variable (EPV) included in a logistic regression model [17]. Therefore, although a speculative logistic regression model that we devised [18] found the SCS, LD and MMI to be independent predictors of mortality (i.e. EPV = 5) this finding may not be valid. We also explored the possible impact ECG-DM might have if it replaced the 12 lead ECG in the SCS. Using the method of Hanley and McNeil [19] we found that in this cohort of patients the SCS had an area under receiver operator characteristic curves (AUROC) for in-hospital mortality of 0.823. Excluding ECG abnormality from the SCS (i.e. subtracting 2 points from the SCS if the ECG was abnormal) reduced the AUROC to 0.819. The coefficients obtained by logistic regression for the SCS adjusted to exclude the ECG suggested that for every 10% increase in MMI the SCS should be increased by one point. When the MMI thus replaced ECG abnormality in the SCS the AUROC increased from 0.823 to 0.850. Although these differences were not statistically significant, the trend is encouraging. Larger studies will be required to confirm this.

This study suggests that ECG-DM might be a practical alternative to the traditional 12 lead ECG required to determine the SCS. Obtaining and interpreting a 12 lead ECG requires time, expertise and expense. In contrast, ECG-DM only takes a few seconds to perform, requires no skill to interpret and is, hence, potentially inexpensive. Although the standard 12 lead ECG is a highly sensitive means of ruling out the risk of in-hospital mortality in acutely ill medical patients [9], the influence of slight ECG abnormalities on mortality risk has not been adequately quantified. MMI, on the other hand, is reported as a continuous variable that increases as the risk of death rises and may, thus, further enhance the discrimination of the SCS.

5. Conclusion

ECG-DM may be a clinically useful predictor of in-hospital mortality. ECG-DM is inexpensive, only takes a few seconds to perform and requires no skill to interpret. Further study to determine its role in the evaluation of acutely ill medical patients is required.

6. Learning points

- ECG dispersion mapping (ECG-DM) is a novel technique that analyzes low amplitude ECG oscillations that only takes a few seconds to perform and requires no skill to interpret.
- The findings of this study suggest that ECG-DM is a useful significant predictor of in-hospital mortality comparable to hypoxia and an elevated white cell count.

Conflict of interest

There is none to declare. Both authors are employees of the Irish Health Service Executive and neither author has any conflict of interest.

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