Impaired Functional Status and Echocardiographic Abnormalities Signifying Global Dysfunction Enhance the Prognostic Significance of Previously Unrecognized Myocardial Infarction Detected by Electrocardiography

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Background: The relationship between electrocardiographic unrecognized myocardial infarction (UMI), abnormal functional status, echocardiographic abnormalities, and mortality has not been evaluated.

Methods: A population-based random sample of 2042 Olmsted County residents, age ≥ 45 years, was studied by self-administered questionnaire, chart review, ECG and echocardiogram, and 5 year follow-up for all-cause mortality. UMI ($n = 81$) was diagnosed if ECG-MI criteria were met without previous documented myocardial infarction. Functional Status was assessed by the Goldman Specific Activity Scale.

Results: UMI subjects had an increased prevalence of abnormal functional status compared to no MI controls (22% vs 11%, $P < 0.05$). This association was independent of sex, obesity, smoking, diabetes, and pulmonary disease. It became insignificant after stratifying for echocardiographic abnormalities. Compared to no MI controls, UMI subjects with impaired functional status had a higher mortality hazard ratio (HR 7.2; $P < 0.0001$) than those without impaired functional status (HR 2.7; $P = 0.02$). In UMI subjects with impaired functional status and any echocardiographic abnormality signifying global ventricular dysfunction (systolic or diastolic dysfunction, left atrial or left ventricular enlargement), the mortality risk was even higher (HR 9.5; $P < 0.001$) and persisted in multivariate analyses. This increased mortality risk was unaffected by adjustment for regional wall motion abnormalities.

Conclusions: The assessment of impaired functional status and echocardiographic abnormalities improves the prognostic significance of UMI. Even in the absence of regional wall motion abnormalities, structural abnormalities of global dysfunction may play a role in mediating the increased mortality associated with UMI.

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myocardial infarction; echocardiography; electrocardiography; epidemiology; prognosis; risk factors

Unrecognized Myocardial Infarction (UMI) is diagnosed by surveillance electrocardiogram in persons in whom there has been no clinically recog-

nized myocardial infarction (RMI). The clinical significance of UMI lies in its cardiovascular mortality, which is equal to that after RMI.¹⁻¹⁰ While

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several studies have emphasized the impaired ability of UMI patients to experience angina,^{1,4,5} the impact of UMI on functional status due to dyspnea or fatigue has not been evaluated. The detection of abnormal functional status in adults is important as it contributes to reduced quality of life and may signify undiagnosed ischemic heart disease. Since UMI is often associated with abnormalities in cardiac structure and function,¹¹ it would be reasonable to hypothesize that UMI subjects would have a higher prevalence of impaired functional status than No MI controls.

The Olmsted County Heart Function Study has identified a population-based community cohort and collected detailed information on symptoms, functional status, echocardiography, and MI status.¹¹ The current analysis was designed to determine the prevalence of abnormal functional status in UMI subjects, to explain abnormal functional status in UMI subjects with abnormalities in ventricular structure and function, and to evaluate the impact of abnormal functional status in UMI subjects on 5 year all-cause mortality, in light of echocardiographic findings.

METHODS

The Mayo Foundation and Olmsted Medical Center Institutional Review Boards approved this study and subjects gave written informed consent.

Study Setting

In 2000, 90% of the 112,255 residents of Olmsted County were white. Other characteristics of this population and its unique resources for population-based epidemiological research have been previously described.¹²⁻¹⁴ Briefly, a population-based sample was randomly selected (with age and sex-specific strata) from Olmsted county, Minnesota. Of the 4203 subjects invited, 2042 (49%) participated. Of the 2042 participants, 7 were excluded because of indeterminate myocardial infarction status and 6 were excluded because of missing information on Goldman Specific Activity Scale. Echocardiographic diastolic function could be determined in 1774 subjects.

Enrollment began January 1, 1997 and ended September 30, 2000. Each subject completed a self-administered questionnaire, underwent a physical examination, and had a 12-lead ECG, echocardiogram and spirometry. The methods have been de-

scribed in detail elsewhere,^{11,12} and included the Rose questionnaire for angina,¹⁵ and systematic medical records' abstraction.¹⁶ Data regarding pulmonary disease was collected by patient self report, by medical record review and by performing spirometry (obstructive lung disease defined as FEV1/FVC <0.70). Myocardial infarction, heart failure and hypertension were diagnosed according to accepted criteria.¹⁷⁻¹⁹ Diabetes was based on the presence of physician diagnosis and treatment in the medical record. Plasma brain natriuretic peptide concentrations were measured by the Biosite assay.¹⁶

Diagnostic Criteria for RMI and UMI

A 12-lead ECG was analyzed according to the Minnesota Code, using the MC-MEANS program.²⁰ The Minnesota Code was selected because it is the commonest ECG analysis system used in previous UMI epidemiological studies,^{2,4,5} and it improves the diagnostic accuracy of Q waves by suppression of Q codes in conditions that produce Q waves in the absence of MI (e.g., pacemaker, Wolfe-Parkinson-White syndrome, left or right ventricular hypertrophy, left or right bundle branch block). Electrocardiographic criteria for prior myocardial infarction included presence of major Q waves (Minnesota Code 1-1-X through 1-2-7), or minor Q waves (code 1-2-8 and 1-3-X) if the ECG also had ischemic ST segment abnormalities (codes 4-1 to 4-3) or ischemic T wave abnormalities (codes 5-2 through 5-3).⁴ If the ECG-MI criteria for prior myocardial infarction were met, but the subject had no recognized clinical infarction by the Gillum criteria,¹⁶ then UMI status was assigned to the subject.

The ECG-MI criteria for prior myocardial infarction were selected based on our previous analysis¹² of the sensitivity and specificity of 6 different ECG-MI criteria that have been used in published UMI studies.^{2,4,5,11,12} A sensitivity analysis of various ECG-MI criteria revealed that although a variation in ECG-MI criteria had an impact of UMI prevalence, it did not have a significant impact on the prevalence of abnormal functional status (22.2% to 23.2%) in UMI subjects, indicating that the association of UMI status with an abnormal functional status is independent of the ECG-MI criteria.^{2,4,5,18} Since the definite ECG-MI criteria used in the Cardiovascular Health Study offer the best combination of sensitivity and specificity, they were adopted for the current analysis.¹²

Determination of Functional Status

All the subjects completed the Goldman Specific Activity Scale, a self-administered questionnaire based on 21 specific activities evaluating dyspnea or fatigue that have known metabolic equivalents of energy expenditure and categorize cardiac functional status into 4 ordinal classes.²¹ Class I activity is approximately equivalent to > 7 METS exercise capacity, Class II to 5-7 METS, Class III to 2-4.9 METS and Class IV to <2 METS. It has been shown to have greater reproducibility and validity than the New York Heart Association functional status classification.²¹ It is easily applicable in clinical settings by asking patients specific questions, for example, "Can you walk down a flight of steps without stopping?" A "No" means less than 4.5 METS. Then he is asked, "Can you shower without stopping?" A "No" means less than 3.6 METS. Then he is asked, "Can you dress without stopping?" (2 METS). A "No" means class IV and a "Yes" means class 3. There are several other activities also listed in order to capture all the subjects.

Echocardiographic Analysis

All patients underwent 2D and M-mode echocardiography following a standardized protocol as previously described.^{22,23} A single echocardiologist (M.M.R.), blinded to the MI status, interpreted all echocardiograms. The echocardiographic variables included ejection fraction, diastolic, regional wall motion abnormality (RWMA) and left ventricular enlargement. Pulsed-wave Doppler examination of mitral (before and during Valsalva maneuver) and pulmonary venous inflow, as well as Doppler tissue imaging of the mitral annulus, was performed. These variables were used to categorize diastolic function as normal, mild dysfunction (impaired relaxation with normal or near normal filling pressures), moderate dysfunction (impaired relaxation with moderate elevation of filling pressures i.e. "pseudonormal filling"), or severe dysfunction (impaired relaxation with marked elevation of filling pressures i.e. "restrictive filling"). For subjects in atrial fibrillation, diastolic function was classified as indeterminate unless restrictive physiology (mitral inflow early velocity < 140 ms) was present. Left atrial enlargement was diagnosed if left atrial diameter (LAD)/body surface area was ≥ 2.3 cm/m² in men and ≥ 2.5 cm/m² in women.²³

Mortality Data

As part of the Rochester Epidemiology Project infrastructure, mortality data on Olmsted County residents are routinely collected by reviewing community medical records, death certificates, and obituary notices. Participants were followed up until death or November 1, 2004, at which time they were censored. This provided 11,210 person-years of follow-up (median follow-up 5.5 years) with 128 deaths. Active surveillance of the first 41% (n = 974) of the cohort recruited to participate in our study identified no additional deaths to those identified via the above mechanisms.²²

Statistical Analysis

Bivariate analysis was conducted by comparing myocardial infarction type (RMI-UMI-No MI) with demographic, clinical, and echocardiographic parameters. For comparison among the 3 groups the following methods were employed: the chi-square test for categorical variables, ANOVA for continuous variables, paired student *t*-test for post ANOVA comparison and Fisher's exact test for post chi-square comparisons. The odds ratio for abnormal (Goldman Class 2-4) versus normal (Goldman Class I) functional status were calculated for the No MI, UMI, and RMI groups. On the basis of our previous observations that echocardiographically determined cardiac structure and function progressively worsens across No MI/UMI/RMI groups, we predicted a similar trend for cardiac symptoms and functional status. A trend test employing logistic regression, and assigning progressively higher category from No MI to UMI to RMI was performed to determine if progressively more abnormal functional status existed in the unadjusted model, and persisted after correction for confounding variables. Both confounding and intervening variables were evaluated using logistic regression and Cox proportional hazard analyses, with the assumption that the resulting ratios (odds ratio of abnormal functional status in UMI or hazard ratios for mortality in UMI) would meaningfully (>10%) diminish after adjustment for these variables. Potential confounders included age, gender, obesity, and pulmonary disease. We evaluated the trend of abnormal functional class after adjusting for echocardiographic abnormalities, with the assumption that echocardiographic abnormalities are intervening variables between MI status and func-

tional status. We postulated that the trend toward abnormal functional status across MI groups would diminish after adjusting for echocardiographic abnormalities, indicating that these are intervening variables.

Cox proportional hazards regression models was used to see if UMI subjects with abnormal functional status had an increased risk of all-cause mortality with or without adjustment for coronary risk factors (confounding variables) as well as echocardiographic abnormalities (intervening variables). The statistical package used was JMP, Version 5 (SAS Institute, Cary, NC, USA) for all the analyses except for stratified analyses where SAS version 8 was used.

RESULTS

Demographic and Clinical Characteristics

Across the No MI-UMI-RMI groups, there was a significant stepwise increase in coronary risk factors, pulmonary disease, cardiac dysfunction, plasma brain natriuretic peptide concentration, and abnormal functional status (Table 1). ECG-based UMI subjects were significantly abnormal in most areas. It is clear from Table 1 that the domi-

nant echocardiographic feature of UMI subjects is diastolic dysfunction (present in the majority of UMI subjects) and not wall motion abnormalities (present in only 12% of UMI subjects)

Functional Status by Specific Activity Scale

The odds ratio for an abnormal functional class in No MI controls was 1.0 (referent), for UMI subjects was 1.73 (CI 1.01, 2.97) (Table 2), and for RMI subjects was 3.8 (P-value for trend <0.0001).

Tables 2 and 3 present stratified analyses of the effect of potentially confounding or intervening factors on the relationship between UMI and functional status. We defined meaningful confounding as a change in adjusted OR across the stratum of a category (e.g., smoking or nonsmoking) of greater than 0.17 or 10% of the crude OR (i.e., adjusted OR of <1.56 or >1.90). By this criterion, confounding did not meaningfully diminish of the relationship between UMI and abnormal functional status by most of the coronary risk factors (sex, smoking, diabetes, or obesity). Even in patient groups with meaningful confounding (age, COPD, self-report emphysema, and hypertension), UMI sta-

Table 1. Baseline Characteristics in No MI, UMI, RMI Patients

	No MI (n = 1847)	UMI (n = 81)	RMI (n = 101)	P Value for Trend
Age*† (years) mean (SD)*†	62 (10)	68 (11)	72 (10)	<0.0001
Male sex*† n (%)†	853 (46.2)	47 (58.0)	?? (74.3)	<0.0001
Current smokers n (%)	170 (9.1)	7 (9.0)	3 (3.0)	0.19
Past smokers n (%)†	746 (40.4)	28 (36)	61 (60.4)	0.005
Obesity n (%)				
(BMI > 30 kg/m ²)	589 (32)	31 (39)	38 (38)	0.1
Diabetes n (%)*	120 (6.3)	9 (16.3)	24 (24.0)	<0.0001
Hypertension n (%)*	511 (27.6)	36 (45)	51 (50.5)	<0.0001
Clinical heart failure n (%)*†	18 (1)	7 (9)	26 (26.0)	<0.0001
Pulmonary Disease				
Physician diagnosed COPD n (%)*	40 (4)	11 (14)	13 (13)	<0.0001
FEV1/FVC <0.7 (%) mean (SD)*	266 (14)	20 (25)	27 (27)	<0.0001
Echocardiographic abnormalities				
Left atrial dimension (cm) mean (SD)*	3.9 (0.61)	4.3 (1.1)	4.4 (0.7)	<0.001
Left ventricular enlargement n (%)*†	239 (13)	16 (19)	53 (52)	<0.001
Regional wall motion abnormality n (%)*†	41 (2)	10 (12)	42 (42)	<0.001
Ejection fraction (%) mean (SD)*†	63 (6)	61 (10)	55 (12)	<0.001
Diastolic dysfunction n (%)*	409 (25)	36 (57)	51 (65)	<0.001
Brain natriuretic peptide (pg/ml) mean (SD)*†	42 (63.6)	85.2 (147)	164 (194)	<0.0001
Abnormal Functional Status*†	262 (11)	18 (22)	39 (39)	<0.001

*UMI vs No MI P = <0.05; †UMI vs. RMI P = <0.05

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume at 1 second.

Numbers and percentages may not match due to missing data and rounding error. Missing information on all the covariates was less than 5% except diastolic dysfunction where it was measurable only on 1776 subjects.

Table 2. Stratified Analysis of Potentially Confounding Variables on the Odds of Abnormal Functional Status in UMI Subjects

	UMI vs No MI Stratum Specific Odds Ratio (CI)	Precision Adjusted Odds Ratio (CI)
Crude odds ratio for abnormal functional status		1.73 (1.01,2.97)
Coronary risk factors		
Stratified for sex*		1.99 (1.15,3.5)
Men	2.02 (0.9,4.7)	
Women	1.97 (0.95,4.1)	
Stratified for age*		1.27 (0.74,2.21)
Age <65	1.88 (0.6,5.5)	
Age ≥65	1.11 (0.6,2.1)	
Stratified for hypertension*		1.50 (0.9,2.6)
Hypertension present	1.24 (0.6,2.7)	
Hypertension absent	1.80 (0.8,4.0)	
Stratified for obesity		1.80 (1.03,3.0)
Obesity present	0.9 (0.4,2.2)	
Obesity absent	2.60 (1.3,5.1)	
Stratified for diabetes		1.60 (0.9,2.8)
Diabetes present	1.50 (0.4,5.4)	
Diabetes absent	1.60 (0.9,3.0)	
Stratified for smoking		1.80 (1.03,3.1)
Current smokers	3.00 (0.6,17)	
Past smokers	2.20 (0.9,5.3)	
Never smokers	1.40 (0.6,2.9)	
Pulmonary diseases		
Stratified for physician diagnosed COPD		1.40 (0.8,2.4)
COPD present	0.54 (0.1,2.0)	
COPD Absent	1.72 (0.9,3.1)	
Stratified for self-report emphysema*		1.55 (0.88,2.72)
Emphysema present	0.45 (0.04,4.82)	
Emphysema absent	1.67 (0.93,2.98)	
Stratified for restrictive lung disease		1.80 (1.05,3.10)
Rest. lung disease present	Indeterminate†	
Rest. lung disease absent	1.80 (1.05,3.10)	
Stratified for asthma (FEV1/FVC<0.7)		1.62 (0.95,2.79)
Asthma present	1.02 (0.36,2.93)	
Asthma absent	1.92 (0.95,2.79)	
Stratified for asthma by self-report		1.61 (0.91,2.86)
Asthma present	1.69 (0.39,7.41)	
Asthma absent	1.60 (0.86,2.97)	

*Adjustment for this variable changes the adjusted OR by more than ± 0.17 (i.e., OR <1.56 or >1.90), suggesting that the crude OR of 1.73 is confounded to a meaningful degree. (see text)

† Indeterminate due to only 20 subjects with restrictive lung disease with zero cell issue.

tus was associated with increased odds for abnormal functional status in the low risk strata (e.g., age <65 or absence of hypertension, COPD, and emphysema). Amongst pulmonary diseases, the association of UMI with abnormal functional status was not confounded by asthma (self report or objectively diagnosed by spirometry) or restrictive lung disease, although confounding was seen in COPD/self report emphysema. The criterion for confounding was a meaningful reduction in the odds ratio, not an actual P value, which would have diminished our ability to evaluate confound-

ing due to the small number of UMI subjects, which is expected given that this is a community-based population and not a hospital-based population.

Among echocardiographic variables, diastolic dysfunction, systolic dysfunction, and RWMA had a meaningful impact on the odds ratio, in the descending order. (Table 3)

There was no evidence for effect modification ($P>0.05$) by any of the variables (Tables 2 and 3) on the relationship between UMI and abnormal functional status.

Table 3. Stratified Analysis of Potentially Intervening Variables on the Odds of Abnormal Functional Status

	UMI vs. No MI Stratum Specific Odds Ratio (CI)	Precision Adjusted Odds Ratio
Crude odds ratio for abnormal functional status		1.73 (1.01,2.97)
Left atrial enlargement		1.68 (0.97,2.91)
LAE present	0.56 (0.16,1.97)	
LAE absent	2.01 (1.04,3.89)	
LAE missing (n = 66)	3.45 (0.69,17.37)	
Left ventricular enlargement		1.65 (0.95,2.89)
LVE present	2.56 (0.84,7.82)	
LVE absent	1.43 (0.75,2.72)	
RWMA*		1.52 (0.90,2.60)
RWMA present	0.54 (0.10,2.90)	
RWMA absent	1.72 (0.96,3.10)	
Systolic dysfunction*		1.40 (0.80,2.50)
EF $\leq$ 50% Present	0.96 (0.30,3.40)	
EF $\leq$ 50% Absent	1.59 (0.90,3.00)	
Diastolic dysfunction*		1.30 (0.70,2.20)
Diastolic dysfunction present	1.18 (0.35,4.0)	
Diastolic dysfunction absent	1.05 (0.53,2.1)	
Diastolic dysfunction missing	1.94 (0.72,5.3)	

*Adjustment for this variable changes the adjusted OR by more than ± 0.173 (i.e., OR <1.56 or >1.90), suggesting that the crude OR of 1.7 is confounded to a meaningful degree. (see text)

In Table 4, we have presented the multiple logistic regression models for the odds of abnormal functional status as a result of UMI or RMI, with trend tests. The first model shows both UMI and RMI to be associated with an abnormal functional status, with a strong trend across MI categories ($P<0.0001$). In both models II (adjusting for potential confounding variables) and III (adjusting for potential intervening, or pathophysiologic cardiac structure and function variables) the trend across MI groups remained significant, but UMI status was no longer independently associated with abnormal functional status.

Mortality Analysis

UMI status was associated with a greater than 3-fold increased risk for mortality, which doubled to 7-fold when UMI subjects with abnormal functional status were considered. (Table 5) After adjustment with standard coronary risk factors, the association of UMI subjects, with or without abnormal functional status, was reduced to borderline statistical significance. However when UMI subjects with abnormal functional status and any echocardiographic abnormality were evaluated, their risk for mortality was even higher at 9 times normal controls and they continued to be significant independent predictors, at more than 3-fold

higher risk, of mortality after adjustment for standard coronary risk factors. This statistically significant association was independent of the presence of regional wall motion abnormalities.

DISCUSSION

In this population-based study, there was a step-wise increase in the prevalence of coronary risk factors, echocardiographic ventricular function abnormalities, cardiac symptoms, physical examination abnormalities, and abnormal functional status from No MI to UMI to RMI patients. The association between UMI status and reduced functional capacity was independent of sex, obesity, smoking, and diabetes. The association of UMI with abnormal functional status was attenuated when adjusted for echocardiographic abnormalities reflecting ventricular dysfunction. UMI subjects with impaired functional status had a higher mortality hazard ratio (HR 7.2) than did UMI subjects with normal functional status (HR 2.7). In UMI subjects with impaired functional status and any echocardiographic ventricular dysfunction (systolic or diastolic) the mortality risk was even higher (HR 9.5). The prognostic significance of ECG diagnosing UMI is significantly amplified if it is associated with impaired functional status and echocardiographic abnormalities.

Table 4. Multiple Logistic Regression Models Examining the Relation of Myocardial Infarction Status to the Odds of Abnormal Goldman Specific Activity Scale Functional Status

Model and Myocardial Infarction Status	Total (n = 2029) OR (95% CI)	P Value
I. Model with MI status only		
No MI	1.00	
UMI	1.73 (1.003,2.95)	0.047
RMI	3.80 (2.48,5.78)	<0.0001
Trend across categories*	1.92 (1.57,2.35)	<0.0001
II. Model with MI status + age, sex, and pulmonary disease		
No MI	1.00	
UMI	0.92 (0.47,1.67)	0.78
RMI	2.37 (1.39,3.99)	0.001
Trend across categories	1.44 (1.12,1.85)	0.005
III. Model + age, sex and echocardiographic dysfunction		
No MI	1.00	
UMI	0.95 (0.43,1.95)	0.9
RMI	2.26 (1.20,4.17)	0.01
Trend across categories	2.02 (1.10,3.63)	0.02

All abbreviations as in Table 1.

*Testing for curvature was performed and found to be insignificant.

Abnormal Functional Status in UMI subjects – Analysis of Confounding Variables

Although the higher prevalence of pulmonary disease in UMI subjects (Table 1) suggested that dyspnea in this group may be due to pulmonary disease instead of UMI, stratified analyses (Table 2) refute this interpretation and show that abnormal functional status due to dyspnea or fatigue in UMI patients is not explained by many of the potential confounders (Table 2). Rather, it appears to be explained by the extent of echocardiographically demonstrable ventricular dysfunction (Table 3). The association between UMI and abnormal functional status was not confounded by self report asthma (odds ratio 1.60 in either strata), but was nullified in those without asthma when asthma was diagnosed objectively by spirometry using the diagnostic criteria of <0.70 of FEV1/FVC ratio. This discrepancy between self-report asthma and objectively diagnosed asthma suggests that some of the UMI patients are misdiagnosing themselves with asthma, when in reality they may not have asthma and their dyspnea is due to UMI. Since breathlessness has previously been shown to increase the risk of future ischemic heart disease in men by more than 2-fold previously,²⁴ our study extends this observation by making a case for con-

sidering ECG-diagnosed UMI as a potential cause of abnormal functional status in patients with pulmonary disease, even if the echocardiogram does not show regional wall motion abnormalities.

The lower prevalence of diabetes in UMI subjects (as compared to RMI) speaks against the commonly held belief that the absence of symptoms in UMI subjects is due to diabetic neuropathy. Rather, it is the lesser degree of cardiac dysfunction that is associated with fewer symptoms and functional status abnormalities. Although angina has been extensively studied in UMI subjects, the novelty of this study is in demonstrating for the first time that ECG-based UMI is associated with an abnormal functional status. Since the advent of echocardiography, an ECG-based UMI, if not associated with regional wall motion abnormalities, is often interpreted as a false positive ECG MI diagnosis. This study demonstrates that in the cross-sectional setting, ECG-based UMI is associated with an abnormal functional status even in those without RWMA (Table 3). In addition the data show that in the prospective setting, UMI subjects with abnormal functional status and echocardiographic abnormalities other than RWMA are independent predictors of all-cause mortality (Table 3 and 5). This call into question the current clinical practice of using echocardiography as the gold standard for diagnosis of prior MI. Even in RMI, more than 50% of RWMA

Table 5. Cox Proportional Hazard Analysis of All Cause Mortality as a Function of ECG-UMI with and without Echo Abnormalities Compared Against No MI Controls

Outcome (All cause mortality)	Model	No MI	UMI Hazard Ratio (95% CI)	P Value
UMI (n = 81)	ECG-UMI alone	1.0	3.67 (2.00,6.22)	0.0001
	ECG-UMI + age + sex + diabetes + hypertension + smoking	1.0	1.82 (0.97,3.26)	0.059
UMI with normal functional status (n = 63)	ECG-UMI with normal functional status	1.0	2.66 (1.19,5.15)	0.019
	ECG-UMI with normal functional status + age + sex + diabetes + hypertension + smoking	1.0	1.51 (0.66,2.96)	0.29
UMI with abnormal functional status (n = 18)	ECG-UMI with abnormal functional status	1.0	7.16 (2.79,15.02)	<0.0001
	ECG-UMI with abnormal functional status + age + sex + diabetes + hypertension + smoking	1.0	2.51 (0.96,5.44)	0.06
UMI with abnormal functional status and any echo abnormality (n = 12)	ECG-UMI with abnormal functional status with any echo abnormality	1.0	9.46 (3.33,21.01)	0.0003
	ECG-UMI with abnormal functional status with any echo abnormality + age + sex + diabetes + hypertension + smoking	1.0	3.43 (1.16,8.17)	0.029
	ECG-UMI with abnormal functional status with any echo abnormality except RWMA (n = 12) + age + sex + diabetes + hypertension + smoking	1.0	3.43 (1.16,8.17)	0.029

disappear with time (Table 1). The novelty of these data is in identifying a subset of subjects with ECG-UMI (those with abnormal functional status and any echocardiographic abnormality) who have increased mortality risk.

Different clinical entities would have different effects on the functional status and therefore they are best studied one variable at a time, as we have done in Tables 2 and 3. There is no meaningful reduction in odds ratio of abnormal functional status in UMI subjects in several clinical entities, which otherwise may themselves produce an abnormal functional status. For example a clinician may disregard an abnormal functional status in an obese patient or a smoker as both entities produce an abnormal functional status. Our results show that it would be a mistake as UMI is associated with an abnormal functional status, even after adjusting for obesity or

smoking, therefore a better way would be to do an ECG to detect an UMI in these subjects. Evaluating this relationship in specific clinical subsets is clinically meaningful and appeals to a clinician, rather than lumping everything together as baseline clinical variables, which can vastly differ from study to study.

Abnormal Functional Status in UMI – Analysis of Intervening Variables

Systolic dysfunction and regional wall motion abnormalities were associated with a meaningful impact on the relationship between UMI and abnormal functional status (OR 1.4 and 1.52, respectively) supporting the hypothesis that systolic dysfunction contributes to abnormal functional status in UMI patients. However, in strata without

systolic dysfunction or regional wall motion abnormalities, UMI status was still associated with higher odds of abnormal functional status, indicating that UMI status may lead to an abnormal functional status through an alternate pathway. This alternate pathway appeared to be diastolic dysfunction as UMI subjects did not have increased odds of abnormal functional status in either strata of diastolic dysfunction. Indeed, amongst echocardiographic variables the maximum impact on the relationship between UMI and abnormal functional status was by diastolic dysfunction (OR = 1.3), an early manifestation of many cardiac diseases including ischemic heart disease.²⁰ It is possible that diastolic dysfunction is an intervening pathophysiologic variable contributing to abnormal functional status for UMI patients.

The multivariate analyses in Table 4 suggested that both confounding variables (Model II) and intervening variables (Model III) have an equivalent impact on the relationship between UMI and functional status. Given the limitations of our sample size and the exploratory nature of our analyses, a definitive answer cannot be given regarding the relative significance of either group of variables on the functional limitations of UMI patients.

Increased Mortality in UMI Subjects with Abnormal Functional Status is Independent of Wall Motion Abnormalities

In contrast to the common clinical practice of discounting ECG-UMI as a false positive if echocardiography does not demonstrate regional wall motion abnormalities, our ECG-UMI subjects had increased risk for mortality independent of RWMA (Table 5). There is a progressively higher relative risk of mortality going more than 3 times normal (HR 3.7) from ECG UMI alone, to more than 7 times (HR 7.16) normal in those UMI subjects with abnormal functional status, to more than 9 times (HR 9.46) normal in those with ECG-UMI, abnormal functional status and any echo abnormality. ECG-UMI is associated with increased mortality even in those with a normal functional status, arguing against the assumption that the increased mortality seen is a function of abnormal functional status alone. ECG-UMI was not associated with increased mortality (HR = 0.99) if the echocardiogram was completely normal, indicating that the increased mortality of ECG-UMI may

be mediated via echocardiographic abnormalities, or these echocardiographic abnormalities may be coincidental findings in UMI subjects and the increased mortality is seen mainly due to echocardiographic abnormalities. It is noteworthy that many of these echocardiographic abnormalities like diastolic dysfunction and left atrial enlargement do not lead to initiation of treatment. However, based on these data, a case can be made for initiating secondary coronary prevention if they are accompanied by ECG-UMI.

Adjustment for coronary risk factors made the association between ECG-UMI and increased mortality of borderline insignificance ($P = 0.06$), indicating the confounding effect of these variables. However when we evaluated those subjects with ECG-UMI, abnormal functional status and abnormal echocardiograms (last 3 subsets in Table 5), these subjects continued to be associated with more than 3 times higher risk of mortality than normal population, even after adjusting for standard coronary risk factors. It is probably this subset which is the most deserving of further attention in terms of instituting secondary coronary preventive measures. It is possible that ECG-UMI may reflect myocardial infarctions of such small magnitude that they do not lead to detectable regional wall motion abnormalities (below the detection threshold of echocardiography), but they do lead to post MI ventricular remodeling characterized by ventricular enlargement, atrial enlargement, systolic and diastolic dysfunction. Therefore, amongst subjects with UMI and abnormal functional status a case can be made for aggressive evaluation and therapy even if an echocardiogram displays only nonspecific findings of ventricular dysfunction.

Strengths and Limitations

In this study random population-based sampling has minimized spectrum bias. The independent reading of electrocardiograms, pulmonary function tests and echocardiograms by different individuals blinded to all clinical data removes interpretation bias and avoids context bias. The low prevalence of missing data in the main outcome variable (functional status) and exposure variable (MI status) minimizes the bias introduced by missing data. Although we have limited number of subjects in the exposure variable, the application of rigorous diagnostic criteria (WHO criteria for RMI, sensitivity analysis of several ECG-MI criteria for UMI and

using medical record review instead of patient recall in ruling out an RMI to diagnose a UMI) make the results meaningful.

The limitations include use of prevalent UMI instead of incident UMI. Cause-effect inferences would have been stronger if our data allowed evaluation of incident UMI, leading to abnormal functional status, which would eventually translate into increased mortality. It may be argued that the ECG-based diagnosis of UMI runs the risk of misclassification bias, which may be reduced by using a more accurate test like echocardiogram, nuclear scan, or MRI to detect an UMI. Nevertheless, it is noteworthy that all the epidemiologic studies conducted on UMI to date have utilized ECG for the diagnosis and have demonstrated that UMI patients have a prognosis as poor as that of RMI patients.¹⁻⁷ Also, as ECG continues to be the most commonly used screening and diagnostic tool in cardiac diseases, it remains highly relevant to clinical practice. The specificity of 96% of ECG to detect prior MI indicates that 4% of No MI subjects will be diagnosed as UMI and the sensitivity of 30% indicates that 70% of UMI subjects will be misclassified into No MI group. Both of these misclassification errors lead to lessening of the echocardiographic differences in between No MI and UMI groups. This creates the need for better ECG diagnostic criteria for myocardial infarction, as well as use of potentially more accurate methods to detect prior UMI, i.e., sestamibi images or MRI. However at present both imaging methods are cost prohibitive and under developed for this purpose. Participation bias, a potential concern, has been addressed by showing that the baseline characteristics (coronary risk factors and coronary heart disease) were similar between participants and nonparticipants.²⁵ The Olmsted County population is predominantly white, reducing the generalizability to other demographic groups.

CONCLUSION

UMI diagnosis by ECG identifies a subgroup of community dwelling adults who are significantly abnormal in regard to functional status. The mortality risk is doubled in UMI subjects with abnormal functional status and is even higher in those with echocardiographic abnormalities signifying global dysfunction, even in the absence of regional dysfunction. Persons diagnosed with ECG UMI should undergo further assessment for functional status determination and echocardiographic evaluation,

including but not limited to detection of wall motion abnormalities. An abnormality in both identifies a high risk subset of UMI patients, who deserve serious consideration for secondary coronary prevention. The most prevalent echocardiographic abnormality in subjects with UMI is diastolic dysfunction, which adds to the ongoing debate regarding diastolic dysfunction being a benign aging finding versus being a pathologic entity. The potential clinical implication of these data is in considering ECG-MI to be a true positive UMI, in the presence of diastolic dysfunction, thereby instituting secondary coronary prevention with aspirin, beta-blockers, and ACE Inhibitors, as none of these patients would otherwise qualify for these therapies with proven benefits for postmyocardial infarction patients.

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