Left ventricular function and heart failure in myocardial infarction: impact of the new definition in the community

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Abstract

Objectives—To evaluate ventricular function and the occurrence of HF among persons with MI meeting only troponin criteria compared to persons meeting CK-MB criteria.

Background—The 2000 ACC/ESC MI definition enabled identification of MIs meeting only troponin-based criteria. Data on ventricular function and HF among these are lacking.

Methods—Between 11-2002 and 05-2006, we prospectively identified 835 MIs in the community using standardized criteria including cardiac pain, ECG and biomarkers. Troponin and CK-MB were prospectively measured in all; each patient was classified according to the criteria met.

Results—We performed echocardiograms (median of 1 day post-MI) in 482 patients (age 68 ± 15 years; 45% women); 363 patients met CK-MB criteria while 119 met only troponin criteria. The latter had lower wall motion score index (1.3 ± 0.4 vs 1.5 ± 0.5 for CK-MB; $p < 0.01$). Diastolic dysfunction was similar in both groups. After one year of follow up, 142 patients developed post-MI HF. Patients meeting only troponin criteria had a lower risk of HF after adjustment for age, sex, comorbidity (HR 0.56, 95% CI 0.37, 0.85, $p < 0.01$), which persisted after further adjustments for systolic or diastolic function.

Conclusions—In the community, the prospective application of the new MI definition identifies patients meeting only troponin criteria with better systolic function than cases meeting CK-MB criteria. Such MIs have a lower risk of subsequent HF. These findings are important for risk stratification in clinical practice.

Keywords

Community; Myocardial infarction; Heart failure; Prognosis

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The American College of Cardiology/European Society of Cardiology (ACC/ESC) diagnostic criteria for myocardial infarction (MI) combines ischemic symptoms with changes in the electrocardiogram and with biochemical markers of myocardial necrosis, emphasizing the use of troponins which are more sensitive and specific than other biomarkers on detecting myocardial injury (1,2). Troponin allows the detection of small amounts of tissue injury that would have gone undetected by creatinine kinase and its MB fraction (CK-MB) (1–3). This biomarker change was expected to have two key consequences: to increase the number of MIs and to shift the clinical spectrum of the disease (4). Indeed, the implementation of the new definition in the community resulted in a large increase in the number of cases of MI (5). Less is known about implications on the clinical spectrum of the disease. Cases identified as MI by the new definition are lacking data on left ventricular systolic and diastolic function. Further, while mortality among cases meeting only troponin-based criteria is lower than mortality among cases meeting CK-MB criteria (5), the occurrence of HF among these is not known.

Despite the controversy (4,6) that surrounded the publication of the new criteria, few studies have prospectively evaluated its impact. Indeed, most of the current knowledge is based on convenience samples and case series that used different assays and diagnostic criteria that were often incompletely standardized. In the present study, we sought to specifically evaluate parameters of left ventricular function among patients with MI and measure the occurrence of post-MI heart failure (HF) to assess differences between cases meeting troponin-based criteria and cases meeting both troponin and CK-MB criteria.

Methods

Study population

Olmsted County, Minnesota, is relatively isolated from other urban centers, and nearly all medical care in virtually every specialty is delivered to residents by few providers, which include the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and a few private practitioners. Each provider in the community uses a unit medical record in which details of care for a patient, regardless of setting, are available in one place. The records are easily retrievable because Mayo Clinic maintains extensive indices that through the Rochester Epidemiology Project are extended to the records of other health care providers in the county, resulting in the linkage of all medical records from all sources of care through a centralized system (7). This provides a unique infrastructure to analyze disease outcomes. Of particular importance for the present study is the availability of information on all episodes of HF including those confined to the outpatient setting.

Ascertainment of MI

All Olmsted County residents hospitalized between November 2002 and May 2006 presenting with a troponin T value greater than or equal to 0.03 ng/mL were prospectively identified within twelve hours of the blood draw through the electronic files of the Department of Laboratory Medicine. Consent was sought from patients or the next of kin (if a patient could not grant consent) to perform a transthoracic echocardiogram and to measure CK-MB in unused serum initially stored for additional clinical need. If serum was not available, an additional blood sample was drawn in connection with a clinically indicated draw whenever possible. Cases underwent serial troponin measurements as part of clinical practice, which did not change during the study period. Troponin was measured at baseline and after symptom onset as recommended (1,2,8), and dynamic changes were used to diagnose MI (5). Peak creatine kinase ratios were used as previously described (9). Troponin T and CK-MB were measured using a sandwich electrochemiluminescence immunoassay on the Elecsys 2010® (Roche Diagnostic Corp; Indianapolis, Indiana). Biomarkers were measured in the laboratories of the Department

of Laboratory Medicine and Pathology, which is certified by the Clinical Laboratory Improvement Act of 1988 and the College of American Pathologists, with all quality control procedures in place.

Three electrocardiograms per episode (first after arrival, last before discharge, and first one after third hospital day) (10) were coded using the Minnesota Code Modular ECG Analysis System (11). Cases were classified using published recommendations based on a combination of cardiac pain, biomarkers, and Minnesota coding of electrocardiograms.(7,11) The reliability of this methodology is excellent.(12)

Clinical data

Killip class was assessed within 24 hours of admission. Comorbidity was measured by the Charlson Index (12). Clinical diagnoses were used to ascertain hypertension, diabetes mellitus, hyperlipidemia, family history of coronary disease (defined as coronary disease in first line male descendants less than 55 years of age and in first line female descendants less than 65 years of age), and smoking.

Echocardiography

In Olmsted County, all echocardiograms are performed at the Mayo Clinic Echocardiography Laboratory. M-Mode, bi-dimensional, Doppler and Doppler tissue imaging were performed according to the guidelines of the American Society of Echocardiography (13). Digital echocardiography data containing a minimum of 3 consecutive beats (5 in atrial fibrillation) were acquired and transferred to a server for storage and archiving (Prosolv Echo Management System, Problem Solving Concepts, Camel, Ind). All echocardiograms were performed at rest early during the index hospitalization and not repeated during follow-up.(14)

Left ventricular ejection fraction (EF) was measured by previously validated methods, including M-mode or bi-dimensional echocardiography using the Quinones formula from the parasternal views (15), by the quantitative bidimensional biplane volumetric Simpson method from 4 and 2 chambers views (13), and bi-dimensional estimate method from multiple echocardiographic views (15,16). EF values were averaged when multiple measurements were performed. As recommended (17), preserved systolic function was defined as an EF greater than or equal to 50%. Left ventricular end-diastolic diameter, interventricular septal and posterior wall thickness were measured by M-mode or bidimensional echocardiography from the parasternal views at end-diastole as recommended by the American Society of Echocardiography, and they were used to calculate left ventricular mass, which was indexed to the body surface area (13).

Diastolic function was assessed by a previously-described approach(18,19) which integrates Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus using the medial annulus velocity (20). This approach enabled classification of diastolic function which was categorized as normal, mild (impaired relaxation without evidence of increased filling pressures), moderate (impaired relaxation with moderate elevation of filling pressures) or severe (advanced reduction in compliance). This classification was previously validated and published (19). Isolated diastolic dysfunction was defined as diastolic dysfunction with EF greater than or equal to 50%.

Follow-up

The complete (inpatient and outpatient) medical record for each participant was reviewed by abstractors unaware of biomarker values. HF, including both in and out-patient events, was validated using the Framingham criteria(21) the reliability of which has been published for Olmsted County studies (22).

Statistical analysis

Continuous variables were summarized as means ± standard deviations and categorical variables as percents. Variables with skewed distributions were presented as medians (25th–75th percentiles). Chi square tests were used to examine the association between type of MI and categorical variables. Rank sum tests were used for continuous variables. Cox proportional hazards regression models were constructed to estimate the unadjusted and covariate-adjusted hazard ratio (HR) and 95% confidence interval (CI) for HF associated with the type of MI. The frequency of missing values was less than 10% except for left ventricular mass which was missing in 22% of the cases. The Institutional Review Board approved the study.

Results

Between November 2002 and May 2006, 835 incident MIs (246 meeting only troponin-based criteria and 589 also meeting CK-MB criteria) occurred in Olmsted County. Among those, 482 underwent echocardiogram prior to hospital discharge and constitute the study population. The mean age of the participants was 68 ± 15 years and 45% were women

Among the participants, 363 (75%) met CK-MB-based criteria and 119 (25%) met only troponin-based criteria. Several key characteristics differed in the two biomarker groups (Table 1). Patients meeting only troponin-based criteria were older, more likely to be women, to have hypertension, greater comorbidities, and non ST elevation MI. They were less likely to present with chest pain, have an anterior MI, or Q-waves on their electrocardiograms than patients meeting CK-MB criteria. Patients diagnosed only by troponin had lower troponin level than those diagnosed by CK-MB.

Echocardiograms were performed at a median (Q1, Q3) of 1 day (1–2 days) post-MI. Systolic dysfunction was present in 33% of the MI patients, while moderate or severe diastolic dysfunction was present in 53% of them. Diastolic dysfunction with preserved left ventricular systolic function was present in 33%. Patients meeting only troponin-based criteria had higher EF (55 ± 14% versus 53 ± 13%, p value 0.01), lower wall motion score index, and smaller end diastolic diameter than cases diagnosed by CK-MB criteria (Table 2). Moderate or severe diastolic dysfunction was equally prevalent in both groups. Other echocardiographic characteristics were similar in both groups. The distributions of left ventricular systolic and diastolic functions differed by MI type (Figure 1).

HF after MI

During a mean follow-up of 0.8 ± 0.7 years, 142 patients developed HF. This corresponds to a one year survival free of HF of 71% (95%CI 67%–75%) with 87% of the HF episodes occurring within the first month post-MI. Among cases meeting only troponin-based criteria, the survival free of HF at one year was 75% (95%CI 68%–84%) compared to 70% (95%CI 65%–75%) among those meeting CK-MB criteria (p= 0.15).

After adjustment for clinical characteristics (age, female sex and comorbidity), MIs meeting solely troponin-based criteria were associated with a large reduction in the risk of post-MI HF (Table 3). The association between troponin-only MI and post-MI HF was unchanged by the addition of EF≥ 50% and moderate or severe diastolic dysfunction. With the addition of wall motion score index or left ventricular end diastolic dimension, this association was slightly attenuated.

In ancillary analyses, we examined the impact of EF as a continuous variable. This analysis yielded similar trends as the main analyses presented herein, thereby attesting to the robustness of our findings.

Discussion

The present study reports the experience of a community with the prospective application of the new MI definition, focusing on left ventricular function and HF. Patients meeting only troponin-based criteria were more likely to have better systolic function than cases diagnosed with the CK-MB criteria. More than half of the patients who experienced an MI had moderate or severe diastolic dysfunction and the presence of moderate or severe diastolic dysfunction was similar in both groups. Compared to persons meeting CK-MB criteria, cases of MI meeting only troponin-based criteria had a substantially lower risk of post-MI HF independent of age, sex, comorbidities, and echocardiographic parameters.

Left ventricular function after MI

The recent literature has underscored the dearth of information on left ventricular function post-MI because ventricular function, by non-invasive or invasive methods, has not been evaluated after MI in routine clinical practice (23). This important caveat notwithstanding, the prevalence of left ventricular systolic dysfunction, when reported, ranged from 27% to 60%. The definitions of left ventricular systolic dysfunction varied greatly across studies thereby explaining the wide ranges of prevalence. However, in studies that used an EF less than or equal to 50% as the cut-off for left ventricular systolic dysfunction, the prevalence of left ventricular systolic dysfunction averaged 50% (23). Importantly, these reports all predated the implementation of the new MI criteria and consisted mainly of clinical trials with their inherent selection biases, such that it is not known whether these numbers are applicable to contemporary cases of MI diagnosed in the community and how this may have changed due to the implementation of the new MI definition. The present population-based study, which defined left ventricular systolic dysfunction as EF less than 50% (17), addresses this gap in knowledge by indicating that in a contemporary cohort that represents the comprehensive experience of a community; one third of MIs have left ventricular systolic dysfunction.

Left ventricular EF may be an imprecise indicator of the degree of myocardial damage as it may be quasi normal despite extensive myocardial damage due to compensatory hyperkinesis in non-infarcted regions (24). Thus, the semi-quantitative assessment of regional systolic function using wall motion score index is important to assess left ventricular systolic function (25,26). Herein, patients diagnosed with MI based on the troponin-only criteria had lower wall motion score index than patients meeting CK-MB criteria.

To the best of our knowledge, there is no published epidemiological data on the prevalence of diastolic dysfunction after MI in the community. In the present community study, more than half of the subjects who experienced an MI had moderate or severe diastolic dysfunction, and the prevalence of moderate or severe diastolic dysfunction was similar between persons with troponin-only MI versus those with CK-MB MI. An informal comparison to prior reports from Olmsted County indicated that overall the prevalence of moderate or severe diastolic dysfunction after MI was higher than noted in a random sample of residents from the population (27) but lower than that reported among persons with HF (28).

HF after MI

Composite evidence from the literature suggests that, after an MI, 30% to 40% of patients will develop HF following admission for the acute event (23). Prior reports from Olmsted County including all patients who experienced an incident MI from 1979 to 1994 diagnosed by the CK criteria indicated that at 5 years 36% had HF (22). In contemporary MI cases, 28% of cases experienced HF at one year of follow up (29), which was similar to that observed in the present series. The present study extends previous reports by indicating that patients with MI meeting

only troponin-based criteria experienced less HF than their counterparts with MI meeting CK-MB criteria.

In the present study, the vast majority of the episodes of HF occurred within the first month post-MI irrespective of the type of MI criteria met. This timing may be related to the early onset of left ventricle remodeling that occurs in the post-MI period (30). Patients meeting troponin-only MI criteria had a lower risk for post-MI HF than patients meeting CK-MB criteria. This observation is congruent with the fact that patients meeting only troponin criteria have better left ventricular systolic function than patients meeting CK-MB criteria, evident by the lower wall motion score index among those with troponin MI compared with the CK-MB MI. However, we reported herein a similar degree of diastolic dysfunction regardless of the type of MI. This suggests that systolic function likely plays a predominant role in the genesis of post-MI HF. These findings are important for risk stratification among these newly identified MIs.

Our data are congruent with the concept that the larger the infarction, the greater the reduction in LV function and the greater the frequency of HF (23). There is evidence in the literature that troponin measurements correlate with infarct size measured with various imaging techniques (31–34). Troponin is acknowledged to be substantially more sensitive than CK-MB (1,2). This will enable the detection of smaller MIs (1,2). Our data indicate that MIs associated with elevations in CKMB are larger than those associated with troponin elevations alone (5). **We previously reported(5) for all participants on the parent study, mortality rates which were higher among patients with MI meeting CK-MB criteria compared to cases meeting only troponin-based criteria. The results seen on the present group were similar (data not shown)**

Strengths and limitations

A focus on left ventricular function post-MI as intended in the present study requires that patients undergo such an assessment. However, in clinical practice in most centers in the US, a substantial proportion of patients with MI do not undergo evaluation of ventricular function early after MI (14,23). Thus, most, if not all, the studies that report on subjects who underwent an imaging examination during the hospitalization for MI reflect this selective practice. **This should be considered, when interpreting the data.**

The internal validity of the present data is quite robust as our study identified all consecutive patients who were then classified according to rigorous validation criteria independently of clinical practice. The racial and ethnic composition of Olmsted County may limit the generalizability of these data to groups under-represented in the population. While no single community can represent the nation, studies of chronic diseases in Olmsted County indicate that results from the county can be extrapolated to a large part of the population.(7) Nonetheless, the present study will need replication in other racial and ethnic groups.

The ability to prospectively examine the impact of the new definition using standardized criteria and consistent assays throughout the study and to evaluate the clinical implications of the redefinition within the same population are unique strengths of the present study. This addresses the stated need for "sentinel centers" that was deemed necessary by the panel of experts to understand the implications of the new definition (4). Indeed, the clinical impact of the redefinition of MI cannot be assessed without the use of standardized, highly reliable criteria.

Conclusions

In the community, the prospective application of the new MI definition indicates that patients meeting only troponin-based criteria had better systolic function than patients diagnosed with the CK-MB criteria. Overall, moderate or severe diastolic dysfunction was present in 53% and similar in both biomarker groups. Compared to persons meeting CK-MB criteria, MI patients meeting only troponin-based criteria had a lower risk of post-MI HF.

Abbreviations list

ACC/ESC, American College of Cardiology/ European Society of Cardiology; CK-MB, creatinine kinase and its MB fraction; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; HF, heart failure; MI, myocardial infarction; Q1, 25th percentile; Q3, 75th percentile.

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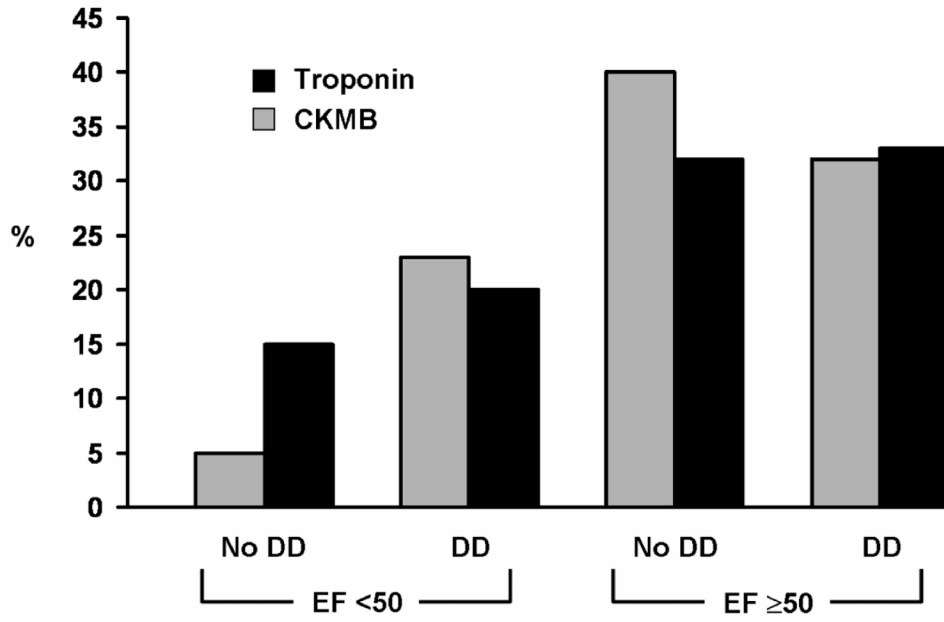
Figure 1. Systolic and diastolic function by MI type
Legend: DD for moderate or severe diastolic dysfunction.

Table 1

Clinical characteristics stratified by the type of biomarker used for MI diagnosis

	Overall (N=482)	Troponin T only (N=119)	CKMB (N=363)	P value
Age, mean ± sd	68 ± 15	71 ± 16	66 ± 15	<0.01
Women, %	45	53	42	0.04
Presence of cardiac pain, %	77	57	83	<0.01
Killip class >1, %	30	25	31	0.22
Hypertension, %	68	77	66	0.02
Hyperlipidemia, %	59	56	60	0.54
Diabetes, %	22	24	22	0.69
Current smoker, %	21	15	23	0.07
Familial CAD, %	16	13	17	0.29
Comorbidity Index				
0, %	34	26	37	
1–2, %	35	32	36	<0.01
3+, %	31	42	27	
Electrocardiogram				
Anterior location, %	42	34	45	0.03
Non ST segment elevation infarction, %	76	94	70	<0.01
Presence of Q waves, %	60	42	65	<0.01
Biomarkers				
Peak ratio of CK				
Tertile 1, %	33	81	22	
Tertile 2, %	33	18	37	<0.01
Tertile 3, %	34	1	41	
CKMB, median (25th–75th percentile), u/L	21 (8–89)	6 (4–9)	41 (14–125)	<0.01
Peak TnT, median (25th–75th percentile), ng/mL	0.7 (0.2–2.6)	0.2 (0.1–0.4)	1.3 (0.3–3.8)	<0.001

Table 2

Echocardiographic characteristics stratified by the type of biomarker used for diagnosis

	Overall (N=482)	Troponin T only (N=119)	CK-MB (N=363)	P value
Wall motion score index, mean ± sd	1.4 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	<0.01
Left ventricular mass index, mean ± sd, g/m^2	104 ± 33	110 ± 39	102 ± 30	0.29
Left ventricular end-diastolic diameter, mean ± sd, mm	49 ± 6	48 ± 7	50 ± 6	0.02
EF >= 50, %	67	71	65	0.20
EF, mean ± sd, %	53 ± 13	55 ± 14	53 ± 13	<0.01
Diastolic dysfunction moderate/severe, %	53	55	53	0.66
Presence of mitral regurgitation, %	44	50	42	0.12

Table 3

Clinical and echocardiographic predictors of post MI HF

Adjustment	CKMB	Troponin	P-value
Unadjusted	1 (reference)	0.75 (0.50, 1.13)	0.17
Age, sex, comorbidity	1 (reference)	0.56 (0.37, 0.85)	0.01
Age, sex, comorbidity, EF > 50%	1 (reference)	0.60 (0.39, 0.91)	0.02
Age, sex, comorbidity, moderate or severe diastolic dysfunction	1 (reference)	0.57 (0.38, 0.86)	<0.01
Age, sex, comorbidity and WMSI	1 (reference)	0.66 (0.43, 1.01)	0.06
Age, sex, comorbidity left ventricular end-diastolic dimension	1 (reference)	0.65 (0.41, 1.03)	0.06

WMSI= wall motion score index