Imaging and Diagnostic Testing

The use of periinfarct contrast-enhanced cardiac magnetic resonance imaging for the prediction of late postmyocardial infarction ventricular dysfunction

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Background Although ejection fraction (EF) both perimyocardial infarction (MI) and late post-MI are important prognostic factors, only implantable cardioverter-defibrillator trials of post-MI patients with depressed late EF have shown improved survival. This may relate to imprecision of early EF because of post-MI stunning. We sought to determine if peri-MI infarct size, as measured by cardiac magnetic resonance (CMR), is superior to early EF to predict late post-MI EF.

Methods Seventy-three patients with ST-elevation MI had infarct size and EF quantified using CMR early (<1 week) and late (>3 months) post-MI.

Results Late EF was significantly correlated with early EF ($R = 0.734$, $P < .001$), and with infarct size ($R = −0.661$, $P < .001$), and both early EF and infarct size were significant predictors of late EF. Subgroup analyses showed that low late EF (≤35%) was better predicted by infarct size than early EF. Half of the patients with early EF ≤35% had a late EF >35%. There was no difference in early EF between the subgroup with a late EF >35% compared to the subgroup with late EF ≤35% (29.7% ± 4.6% vs 28.0% ± 4.9%, $P = .414$). There was, however, a significant difference between these 2 groups in infarct size (22.6% ± 10.8% vs 34.7% ± 7.8%, $P = .011$).

Conclusions Infarct size as determined by CMR immediately post-MI is a significant predictor of late EF and is superior to early EF in patients with initially depressed EF. Further studies are warranted to assess whether infarct size estimation by CMR after acute MI can better identify patients who are at risk for sudden cardiac death than early EF. (Am Heart J 2008;156:498-505.)

The immediate postmyocardial infarction (MI) period is associated with a heightened risk for sudden cardiac death (SCD) that plateaus by 6 to 12 months.[1] Implantable cardioverter-defibrillator (ICD) treatment remote (ie, >40 days) from an MI in patients with left ventricular dysfunction has been shown to reduce total mortality.[2-4] In contrast, in the DINAMIT trial, patients with left ventricular dysfunction 6 to 40 days post-MI who received an ICD did not have a reduction in total mortality.[5] As left ventricular dysfunction has adverse

prognostic significance in both the early post-MI period and remote from the MI, it is unclear why a survival benefit related to ICD therapy is not noted in patients with left ventricular dysfunction early post-MI.

This may be, in part, because of the pathophysiology underlying the method for assessing left ventricular dysfunction, namely the *ejection fraction* (EF). Ejection fraction is affected by many parameters, such as preload, afterload, and contractility[6,7] and often demonstrates significant variation.[8] Yet, because of its relationship to prognosis in populations, it has been widely adopted.

One potential explanation for the lack of ICD benefit in the early post-MI period is that in the setting of remote MI, left ventricular dysfunction likely serves as a surrogate for the presence of significant substrate or scarring, a known risk factor for serious ventricular arrhythmias and SCD.[9-11] In contrast, in patients immediately after an MI, it is possible that low EF does not solely reflect scarring but is also influenced by acute hemodynamic parameters and myocardial stunning.

Because the substrate for life-threatening ventricular arrhythmias is more closely linked to infarct size than EF, this study was undertaken to assess the change in EF after MI and its relation to infarct size measured in the peri-MI period. Because of the multitude of physiologic factors that

may affect the EF determined in the peri-MI period, we hypothesized that acute infarct size, as determined by cardiac magnetic resonance (CMR), is a better predictor of left ventricular dysfunction late post-MI than the peri-MI EF.

Methods

This was a retrospective analysis from an ongoing, prospective cohort study originally designed to examine post-MI remodeling,[12] consisting of patients admitted to Northwestern Memorial Hospital (Chicago, IL) for STEMI between July 1999 and August 2005. Patients were included in the original study population if they had all 3 of the following: chest pain >30 minutes, >1.0-mm ST-segment elevation in 2 contiguous electrocardiographic leads, elevated creatine kinase-MB (CK-MB) levels, and consent for CMR evaluation within 1 week (early) and again at least 50 days after presentation (late). Patients were excluded if they had a history of MI or were unable to undergo CMR because of frequent ventricular arrhythmias, unstable hemodynamics, or other CMR contraindications. Of the 96 patients enrolled, 2 were unable to complete the initial CMR because of claustrophobia, 3 had an ICD placed, and 18 had not yet undergone late CMR. A total of 73 patients met all criteria and were included in the current analysis. All participants gave written informed consent to the study protocol, which was approved by the Northwestern University (Chicago, IL) institutional review board.

Cardiac magnetic resonance

The CMR acquisition was performed using a standard technique described previously.[13] Briefly, CMR was performed in a 1.5T scanner (Siemens, Erlangen, Germany). Functional assessment of the left ventricle was performed without contrast using a cine steady-state free precession sequence. Delayed images were then obtained for infarct quantification starting 10 minutes after the administration of gadopentetate dimeglumine (gadolinium-DTPA; Berlex, Montville, NJ), 0.2 mmol/kg, using a T1-weighted, segmented inversion-recovery, fast gradient-echo pulse sequence.[14] Coverage of the entire left ventricle was acquired with 10-mm spacing, typically 6 to 8 short axis images.

Cardiac magnetic resonance image analysis

The CMR images for each subject were randomized, and identifying data were removed for blinded analysis. Quantitative analysis of left ventricular (LV) mass, end-diastolic volume, end-systolic volume, and EF was performed by an experienced physician by manually tracing the epicardial borders (excluding epicardial fat) and endocardial borders (excluding papillary muscles) at end-diastole and end-systole for all sequential short axis slices using ImageJ (NIH, Bethesda, MD).

Contrast-enhanced CMR images were analyzed to determine infarct and noninfarct LV myocardial volume as described previously.[13] The hyperenhanced infarct area was manually planimetered by visual inspection in each short axis slice, including only regions that were fully enhanced and approximately ≥3 SDs above the mean of normal myocardium.[14-16] Infarct size was reported as a percentage of the total LV myocardial volume. Qualitative segmental wall thickening and transmural extent of infarct analysis was performed using a 17-segment model.[17] A viability score was calculated as the total number of either normal segments or segments with any wall motion abnormalities and hyperenhancement in the same segment <25% wall thickness.

Data analysis

The initial analysis showed that the disparity between early and late EF was systematically larger in the patients with lower EF. We therefore performed 2 additional analyses. In the first analysis, the whole population was divided into 2 groups. Group 1 included the patients with a late EF >35%, and group 2 included those with a late EF ≤35%. In the second analysis, those patients with a low early EF ≤35%, that is, those who might have been eligible for DINAMIT, were evaluated. In this subgroup, we compared infarct characteristics among those in whom late EF improved to >35% versus those in whom EF remained ≤35%.

Results are expressed as mean ± SD, unless otherwise noted. Discrete variables and receiver operating characteristic (ROC) curves were compared across patient groups using the χ^2, Fisher, or Spearman tests, and continuous variables were compared with Students t test or Mann-Whitney U tests, where appropriate. Multivariate binary logistical regression using a model that included early EF and infarct size was performed to identify independent determinants of depressed late EF, and a Hosmer-Lemeshow goodness-of-fit test was used to test for model appropriateness. A 2-tailed P value <.05 was considered statistically significant. All analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL).

Results

Of the 73 subjects, all had successful reperfusion with percutaneous coronary intervention (PCI) within 24-hours of presentation to the hospital except for 2 patients with Thrombolysis In Myocardial Infarction (TIMI) grade 1 flow after PCI and 1 patient who had an unsuccessful PCI attempt of a left circumflex occlusion. In all, 72 patients received intracoronary stents. All patients had significant elevation of creatine phosphokinase-MB (mean 258.5 ± 201 ng/mL). During the period between the initial and follow-up CMR (mean 151 days), 1 patient underwent successive PCI for in-stent restenosis, 1 patient was readmitted for unstable angina with subsequent PCI to other coronary lesions, and 1 patient underwent coronary artery bypass graft. There were no deaths throughout the follow-up period.

The mean number of days from hospital admission to the acute and late CMR was 2.7 ± 2.1 days and 151.3 ± 102.1 days, respectively. All patients had evidence of hyperenhancement on the initial CMR. Infarct size was smaller on the late CMR study (16.3% ± 10.7% vs 20.3% ± 10.9%, $P < .001$).

The average early EF was 41.3% ± 9.6%, and the average late EF was 45.8% ± 9.4% ($P < .001$). The average infarct size was 20.3% ± 10.9%, and the average number of viable segments was 13.4 ± 2.8. Late EF significantly correlated with early EF ($R = 0.734$, $P < .001$) (Figure 1). Late EF was also significantly correlated with infarct size ($R = -0.661$, $P < .001$) (Figure 2), and number of viable segments ($R = 0.419$, $P < .001$). The mean intraindividual difference between early and late EF was 4.5% ± 7.0% (Figure 3). There was a much larger difference between early and late EF among patients with a low early EF compared to

Figure 1
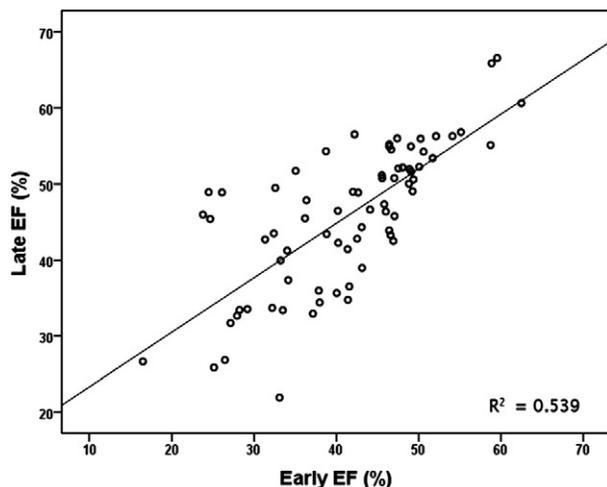
Correlation between early EF and late EF for all 73 patients.

Figure 2
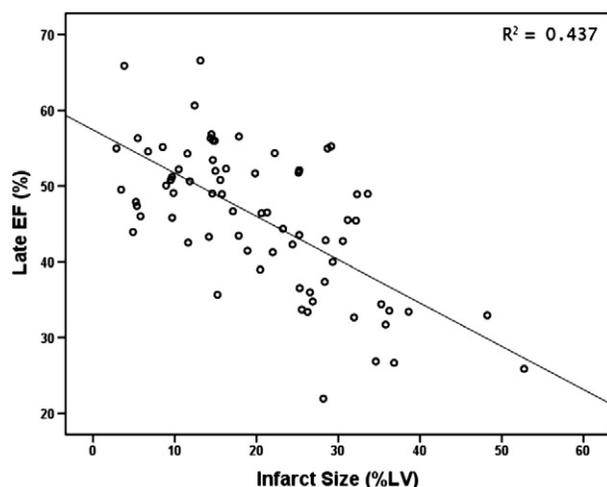
Correlation between infarct size by CMR and late EF for all 73 patients.

those with a more normal EF. By multiple linear regression, both early EF (odds ratio [OR] 0.527 per % change, 95% confidence interval [CI] 0.326-0.703, $P <$ .001) and infarct size (OR -0.330 per % change, 95% CI -0.452 to -0.119, $P < .001$) were independent predictors of late EF, but the number of viable segments was not.

Subgroup analyses

Late EF >35% versus ≤35%. There were 60 patients in group 1 (late EF >35%) and 13 patients in group 2 (late EF ≤35%). Characteristics of these groups are shown in Table I. There were no significant intergroup differences in

Figure 3
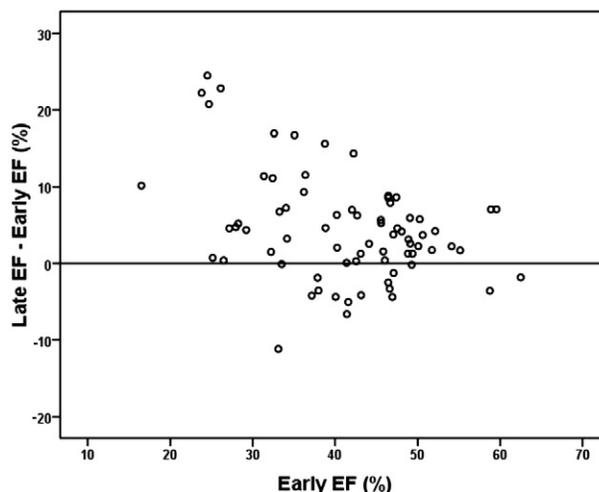
Relation between the same-individual EF change from early post-MI to late, shown on the y-axis, and early ejection fraction on the x-axis.

Table I. Group characteristics

|	Late EF >35% (n = 60)	Late EF ≤35% (n = 13)	Significance
Clinical characteristics			
Male	49 (81.7)	12 (92.3)	0.680
Diabetes mellitus	9 (15.0)	3 (23.1)	0.438
Family history of coronary artery disease	14 (23.3)	5 (38.5)	0.307
Hypertension	25 (41.7)	7 (53.8)	0.451
Hyperlipidemia	29 (48.3)	5 (38.5)	0.485
Tobacco use	30 (50.0)	4 (30.7)	0.189
β-Blocker use	57 (95.0)	11 (84.6)	0.431
Angiotensin-converting enzyme inhibitor use	51 (85.0)	10 (76.9)	0.673
Age (y)	56.9 ± 11.3	54.5 ± 11.2	0.487
Door-to-balloon (min)	110.6 ± 65.5	85.4 ± 31.3	0.082
Early CMR characteristics			
EF (%)	43.7 ± 8.6	30.5 ± 6.5	<0.001
End-diastolic volume (mL)	148.9 ± 34.2	192.6 ± 41.1	0.003
End-systolic volume (mL)	84.6 ± 26.3	135.3 ± 40.6	0.001
CMR total infarct (% LV)	17.1 ± 8.5	35.2 ± 8.1	<0.001
Anterior MI	28 (46.7)	9 (69.2)	0.140
Viable segments (n)	13.9 ± 2.2	11.4 ± 4.2	0.003

Values are expressed as means ± SD or n (%).

age, sex, time to reperfusion, or the presence of diabetes, hypertension, hyperlipidemia, tobacco use, β-blocker use, or angiotensin-converting enzyme inhibitor use.

Figure 4
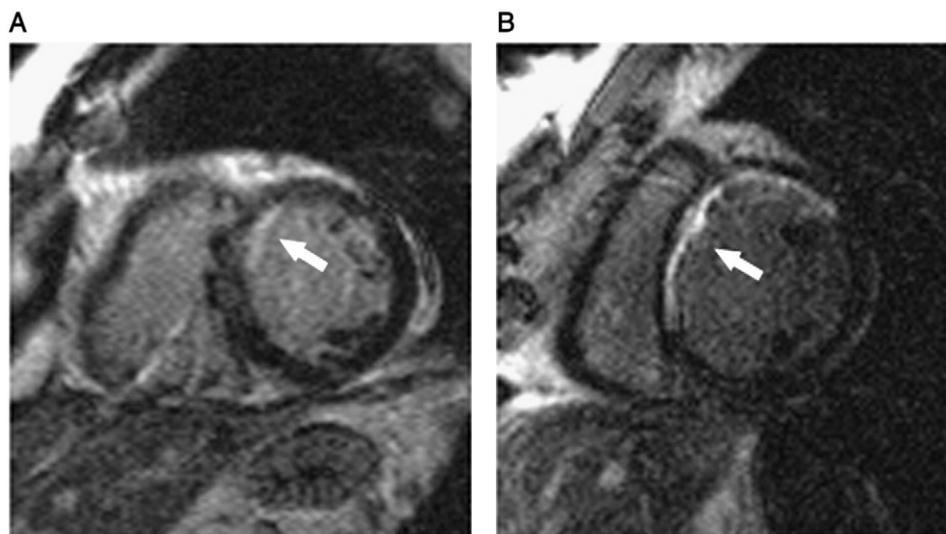
Representative delayed contrast-enhanced short axis CMR images from 2 patients. Arrows indicated hyperenhancement consistent with an anterior myocardial infarction. Patient A and patient B had similar early EF of 26.1% vs 26.5%. However, patient A had an infarct size of 15.8% and a late EF of 48.9%, whereas patient B had an infarct size of 34.6% and a late EF of 26.8%.

Figure 5
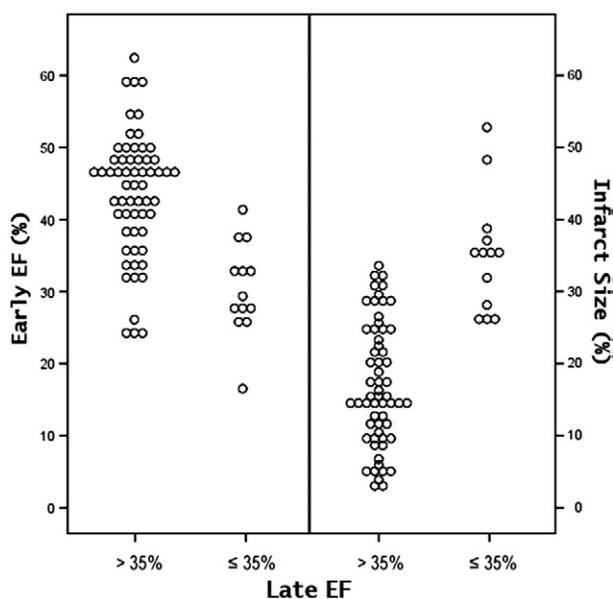
Distribution of infarct size for all 73 patients is shown on the right panel and early EF on the left panel, subdivided by late EF. The y-axis for the right panel is percentage of infarct size of total left ventricular volume, and percentage of EF is shown on the y-axis of the left panel.

Differences in CMR characteristics between the 2 subgroups are shown in Table I. Infarct size was smaller (17.1% ± 8.5% vs 35.2% ± 8.2%, P < .001) and early EF was larger (43.7% ± 8.6% vs 30.5% ± 6.5%, P <.001) in group 1 versus group 2. There were more viable segments on the first CMR in group 1 than group 2 (13.9 ± 2.2 vs 11.4 ± 4.2, P < .04). In addition, the gain in EF for each patient between their 2 studies was greater in group 1 than group 2 (5.3% ± 6.9% vs 0.4% ± 5.7%, P = .01). Figure 4 is an example of 2 patients with similar early EF but different infarct size and late EF. As expected, the correlation of late EF to early EF was stronger in group 1 (R = 0.141, P < .001) than in group 2 (R = 0.059, P = .87).

The distribution of early EF and infarct size in groups 1 and 2 are shown in Figure 5. The ROC curves for acutely measured infarct size as well as early EF to predict late EF >35% are shown in Figure 6. Infarct size had an area under the curve (AUC) of 0.942 with SEM ± 0.028 but was not significantly better than early EF (AUC = 0.885, P = .15). An infarct size of 34% was found to have a specificity of 100% and a sensitivity of 62% (8/13 low late EF cases correctly identified) to predict that patients would have a late EF ≤35%. This corresponds to a positive predictive value of 100% and negative predictive value of 92% in this patient population.

A multivariate binary logistical regression model was created by including 2 of the significant univariate predictors of the outcome (early EF, P < .001 and infarct size, P < .001). In this model, infarct size was significantly and independently associated with late EF ≤35% after adjustment for early EF (OR 1.29 per % change, 95% CI 1.05-1.58, P = .02). Adjustment for early EF did not appreciably change the point estimate of the infarct size OR (OR 1.36 with infarct size alone

Figure 6
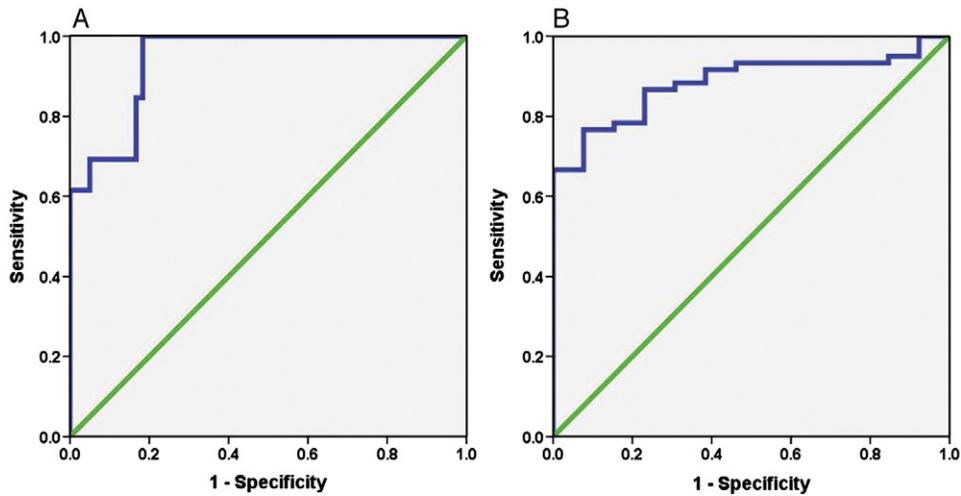
Panel A shows the ROC curve for total infarct size as measured by CMR to predict a late EF of >35% or ≤35%, AUC = 0.942 (CI 0.887-0.997). Panel B shows the ROC curve for early EF to predict late EF, AUC = 0.885 (CI 0.806-0.963).

Table II. Characteristics of the low early EF subgroup

	All patients n = 20	Late EF >35% n = 10	Late EF ≤35% n = 10	P
Acute EF (%)	28.8 ± 4.6	29.7 ± 4.3	28.0 ± 4.9	.41
Late EF (%)	37.2 ± 8.4	44.4 ± 4.1	30.0 ± 4.3	<.01
Improvement in EF (%)	8.4 ± 9.2	14.7 ± 7.7	2.0 ± 5.6	<.01
Infarct size (%)	28.7 ± 11.1	22.6 ± 10.8	34.7 ± 7.8	.01

Values are means ± SD.

in the model vs 1.29 with infarct size and early EF in the model).

In contrast, early EF was no longer significantly associated with late EF ≤35% after adjustment for infarct size (OR 0.92 per % change, 95% CI 0.79-1.07, P = .26). Because of a significant correlation between early EF and infarct size (r = −0.63, P < .01), further tests were performed to assess collinearity. A Hosmer-Lemeshow goodness-of-fit test had a χ^2 of 4.97 (P = .76), indicating appropriate fit of the model with both covariates.

Similarly, another model was created to test for independence of viability, which contained early EF, infarct size, and number of viable segments. In this model, infarct size remained the only significant predictor of late EF (OR 1.30 per % change, 95% CI 1.04-1.63, P < .03).

Early EF ≤35%

There were 20 patients with an early EF ≤35%—10 had an increase in EF to >35% on the late CMR study and 10 did not. Table II shows the characteristics of these

Figure 7

Improvement in Ejection Fraction in a Low EF Peri-MI Subgroup
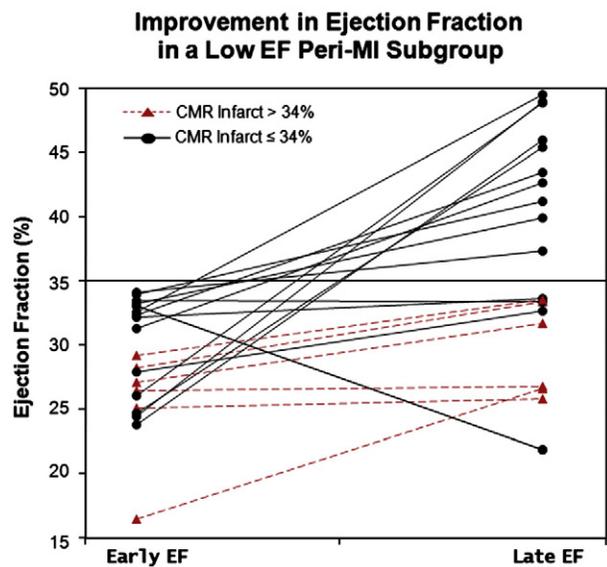
Ejection fraction change in the subgroup with depressed early EF ≤35% (n = 20). Diamonds with dotted lines represent subjects who have an infarct size >34%, and circles with solid lines are those with infarct size ≤34%.

subgroups. The average improvement in EF was 8.4%. There was no difference in early EF between the subgroup with a late EF >35% compared to the subgroup with late EF ≤35% (29.7% ± 4.6% vs 28.0% ± 4.9%, P = .414). There was a difference between these 2 groups in

infarct size on the early CMR study (22.6% ± 10.8% vs 34.7% ± 7.8%, *P* = .011). Individual changes in EF between the early and late CMR are shown in Figure 7. In addition, demonstrated in this figure are all patients with an early infarct size >34%, demarcated by dashed lines. Although half of the patients with an early EF ≤35% had a late EF >35% in this subpopulation, all patients with an infarct size >34% had a late EF ≤35%.

Discussion

The major finding of this study is that infarct size, as determined by early CMR, is a significant predictor of left ventricular dysfunction late post-MI and is superior to early EF in patients whose initial EF is depressed. Importantly, patients with large infarct size immediately post-MI who had a low early EF did not have significant improvement in EF at follow-up. In addition, half of the highest risk, DINAMIT-like patients with an early EF ≤35% showed substantial improvement in EF. In this subpopulation, infarct size on CMR and not early EF identified which patients had improvement in LV function at late follow-up. These data suggest that the prognostic significance of EF measurement immediately peri-MI, particularly for assessment of late risk for SCD, may be limited. Alternative measures, such as infarct size, may be more powerful.

Ejection fraction, measured peri-MI, has important prognostic significance. When EF is measured immediately after MI, there is a striking increase in mortality as EF decreases <40%.[18-20] The present study is consistent with these findings; on a population basis, there is a significant correlation between early EF and late EF. If depressed late EF is an important determinant of SCD, then depressed early EF would also be expected to be an important determinant. However, as shown in Figure 3, the discrepancy between early EF and late EF grows larger as early EF declines. For this reason, infarct size emerges as a better indicator of the substrate that will be responsible for subsequent left ventricular dysfunction and arrhythmia risk. Cardiac magnetic resonance is an ideal modality to compare these 2 metrics; CMR-measured EF has been shown to be accurate as well as having more interstudy reproducibility than echocardiography,[21] and delayed enhancement analysis is reproducible with low inter-observer and intraobserver variability.[22]

There is strong evidence that the early post-MI period is a high-risk period for SCD. The most suggestive and contemporary data come from an analysis of the VALIANT database.[1] The VALIANT trial enrolled patients immediately after a MI with EF ≤40%.[23] The initial 30-day period post-MI had the highest rate of SCD with a monthly event rate of 1.4%. These data show that the early post-MI period is potentially critical for prevention of SCD. Some medications, such as aldosterone-receptor blockers given early post-MI in patients with depressed EF have been

shown to decrease SCD.[24] In contrast, ICD use in high-risk groups immediately post-MI has not demonstrated benefit.[5,25] In the DINAMIT trial, patients with an MI within the previous 40 days and EF ≤35% (and elevated heart rate or diminished heart rate variability) were randomized to ICD or standard therapy.[5] After 4 years, there was no difference in overall mortality between the 2 groups. Although the reported rate of arrhythmic death decreased in the ICD arm, the rate of nonarrhythmic cardiac death was higher. The authors suggested that early after an acute MI, appropriate ICD therapy does not reduce mortality and merely identifies patients at higher risk of dying from heart failure.

The DINAMIT authors evaluated follow-up EF in a portion of their study population. Less than half had a follow-up EF, with a mean increase in EF of 2% ± 11%. In the present report, we also noted a low average improvement in EF (4%) over the entire study population and a slightly higher improvement (8%) in the subgroup with low initial EF. Although the group means do not change substantially, individual changes in EF are significant and are best predicted by initial infarct size. In the current study, half of the patients with early EF ≤35% had a late EF >35%. Given the improved EF in this latter group, it is possible that they have a substantially lower risk of SCD; including them in an ICD trial therefore reduces the statistical power to detect a benefit. Although there may be multiple reasons why an ICD intervention early after a MI may not improve survival, our data suggest that a low EF identified at this time will select a significant percentage of patients whose EF improves to a range associated with a lower risk for arrhythmic sudden death.

Because of its ease of measurement and demonstrated prognostic significance in multiple settings,[19,26] including immediately post-MI, EF has emerged as a major tool for risk stratification. However, it is well known that there are many physiologic factors that may affect the measurement of EF, including preload, afterload, and contractility. In addition, differences in infarct healing between patients because of a variety of metabolic and genetic factors may lead to difficulty predicting late ventricular function from early EF.[27]

A portion of the improvement that may occur in some cardiac segments that have depressed function immediately post-MI may be because of cardiac hibernation or stunning, the extent of which can be assessed by scar quantification and wall motion analysis on CMR. The transmural extent of delayed enhancement with gadolinium within the LV wall has been previously shown to correlate well with functional recovery of that myocardial region after elective coronary revascularization[15] as well as in the acute MI setting.[28-30] Although our data show a significant relation between late EF and number of viable segments, this relationship was not independent of early EF or infarct size. This suggests that while myocardial stunning may be one of the mechanisms by which LV function recovers after acute MI, it does not

appear to fully predict overall functional recovery, which may also be modulated by genetic, metabolic, or other differences in infarct healing.

Infarct characterization by CMR may also be a powerful tool for the prediction of ventricular arrhythmia. Patients with increased amounts of delayed enhancement are more likely to have inducible ventricular arrhythmias with electrophysiology study (EPS). Bello et al[31] performed CMR on 48 patients with coronary artery disease before EPS. Patients with increased infarct mass and infarct surface area were more likely to have inducible monomorphic ventricular tachycardia on EPS, with better predictability than EF. Recent data have shown that quantification of the periinfarct zone by CMR can predict increased mortality, presumably via an arrhythmic mechanism,[32,33] and also inducibility of monomorphic ventricular tachycardia on EPS.[34] These studies support the notion that infarct characterization by CMR can be used as a predictor for arrhythmic risk.

Limitations

This study did not assess the use of EF and infarct size as risk predictors of mortality. In fact, there was no mortality in this medically well-treated population at a mean follow-up time of 151 days. Thus, we were only able to assess the use of early post-MI measurements to predict left ventricular dysfunction late post-MI, a known risk factor for arrhythmic sudden death. Large scale studies will be required to determine whether early post-MI infarct size is a better predictor of arrhythmic sudden death than early post-MI EF.

Conclusion

Based on these data, it is possible that identification of patients with large infarct size early post-MI can be a supplemental strategy for assessing increased risk for SCD rather than solely evaluating EF. If so, these patients can appropriately be selected for more aggressive prevention of SCD. The nature of this treatment, however, is not yet clear. DINAMIT and others[5,25] have demonstrated that early post-MI EF, even in conjunction with other markers, is an inadequate selection tool to predict who is at high risk for SCD that is preventable by an ICD. Either the marker (EF) is inadequate or the treatment (ie, ICD) is ineffective in this particular period. Further studies to evaluate the effectiveness of early post-MI therapy for prevention of SCD based on infarct size would shed light on the use of CMR infarct size quantification for risk stratification.

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