

Impact of Right Ventricular Involvement on Mortality and Morbidity in Patients With Inferior Myocardial Infarction

Shamir R. Mehta, MD, FACC,*† John W. Eikelboom, MBBS, FRACP,†
 Madhu K. Natarajan, MD, FACC,*† Rafael Diaz, MD, FACC,‡ Cheelong Yi, MSc, PhD,†
 Raymond J. Gibbons, MD, FACC,§ Salim Yusuf, DPHIL, FACC*†

Hamilton, Canada; Rosario, Argentina; and Rochester, Minnesota

OBJECTIVES	We sought to evaluate the prognostic impact of right ventricular (RV) myocardial involvement in patients with inferior myocardial infarction (MI).
BACKGROUND	There is uncertainty regarding the risk of major complications in patients with inferior MI complicated by RV myocardial involvement. Whether these complications are related to RV myocardial involvement itself or simply to the extent of infarction involving the left ventricle (LV) is also unknown.
METHODS	We examined the incidence of death and mechanical and electrical complications in patients with (n = 491) and without (n = 638) RV myocardial involvement and in patients with anterior MI (n = 971) in an analysis from the Collaborative Organization for RheothRx Evaluation (CORE) trial. Left ventricular infarct size was assessed by technetium-99m-sestamibi single-photon emission computed tomography and peak creatine kinase, and LV function was assessed by radionuclide angiography. We also performed a meta-analysis in which we pooled the results of our study with previous smaller studies addressing the same question.
RESULTS	Six-month mortality was 7.8% in inferior MI compared with 13.2% in anterior MI. Among patients with inferior MI, serious arrhythmias were significantly more common in patients with RV myocardial involvement who also had a trend toward higher mortality, pump failure and mechanical complications. However, this was not associated with a difference in LV infarct size or function. A meta-analysis of six studies (n = 1,198) confirmed that RV myocardial involvement was associated with an increased risk of death (odds ratio [OR] 3.2, 95% confidence interval [CI] 2.4 to 4.1), shock (OR 3.2, 95% CI 2.4 to 3.5), ventricular tachycardia or fibrillation (OR 2.7, 95% CI 2.1 to 3.5) and atrioventricular block (OR 3.4, 95% CI 2.7 to 4.2).
CONCLUSIONS	Patients with inferior MI who also have RV myocardial involvement are at increased risk of death, shock and arrhythmias. This increased risk is related to the presence of RV myocardial involvement itself rather than the extent of LV myocardial damage. (<i>J Am Coll Cardiol</i> 2001;37:37-43) © 2001 by the American College of Cardiology

Patients with inferior myocardial infarction (MI) who have right ventricular (RV) myocardial involvement appear to have a worse prognosis than those who do not have RV involvement (1-3). However, previous studies have been limited by small patient numbers, which has made it difficult to obtain reliable estimates of the risk of important complications, such as mortality, mechanical complications (e.g., left ventricular [LV] failure and cardiogenic shock) and serious ventricular arrhythmias. Furthermore, it remains unclear whether the adverse prognosis in patients with RV myocardial involvement is simply a reflection of more extensive LV infarction or whether it may be due to the presence of RV myocardial involvement itself.

To address these two issues, we examined the incidence of death, cardiogenic shock, ventricular arrhythmias and atrioventricular block in patients with (n = 491) and without (n = 638) RV myocardial involvement and in patients with anterior MI (n = 971) enrolled in the Collaborative Organization for RheothRx Evaluation (CORE) trial. We then pooled our results with previous smaller studies of RV myocardial involvement to obtain more reliable estimates of risk. We also assessed LV infarct size by technetium-99m (^{99m}Tc) single-photon emission computed tomography (SPECT) and peak creatine kinase (CK), as well as LV function by radionuclide angiography (RNA), to determine whether these complications were related to more extensive LV damage or to the presence of RV myocardial involvement itself.

METHODS

Patients. The CORE trial was a multicenter, randomized, double-blind, placebo-controlled trial of 2,948 patients with acute MI who were randomized to receive RheothRx or placebo. The inclusion and exclusion criteria, study inter-

From the *Division of Cardiology, Hamilton Health Sciences Corporation, McMaster University, Hamilton, Canada; †Population Health Institute, McMaster University, Hamilton, Canada; ‡Estudios Cardiológicos Latinoamerica, Rosario, Argentina; and §Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minnesota. Drs. Mehta and Eikelboom were recipients of Heart and Stroke Foundation of Canada Research Fellowship Awards. Professor Yusuf is the recipient of a Medical Research Council of Canada Senior Scientist Award and holds a Heart and Stroke Foundation of Ontario Research Chair.

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Abbreviations and Acronyms

CK	= creatine kinase
CORE	= Collaborative Organization for RheothRx Evaluation trial
LV	= left ventricle or ventricular
MI	= myocardial infarction
RNA	= radionuclide angiography
RV	= right ventricular
^{99m} Tc-sestamibi SPECT	= ^{99m} Technetium Sestamibi Single-Photon Emission Computerized Tomography
VF	= ventricular fibrillation
VT	= ventricular tachycardia

ventions and primary efficacy outcomes have been previously published (4). Briefly, patients presenting within 12 h of symptom onset and with at least 1-mm ST segment elevation in two or more contiguous leads or with new left bundle branch block were eligible for inclusion. Patients undergoing primary percutaneous transluminal coronary angioplasty or with renal impairment (creatinine >2.5 mg/dl) were excluded. All patients gave written, informed consent, and the study protocol was approved by the local Institutional Review Boards.

Right ventricular involvement. Myocardial infarction was diagnosed by at least 1-mm ST segment elevation in at least two contiguous leads on the baseline electrocardiogram (ECG): leads V₁ through V₄ for anterior MI and leads II, III and aVF for inferior MI. At the time of the baseline ECG, all centers were prospectively instructed to record lead V_{4R} in patients with ST segment elevation in leads II, III or aVF. Right ventricular myocardial involvement was diagnosed if there was at least 1-mm ST segment elevation in lead V_{4R} within 12 h of symptom onset. Of 1,599 patients randomized with acute inferior MI, 1,129 (71%) had lead V_{4R} analysis performed; RV status was unknown in the remaining 470 patients (29%).

LV infarct size and ejection fraction. A subset of clinical centers participating in the CORE trial performed additional laboratory studies to assess LV infarct size by ^{99m}Tc-sestamibi SPECT, as well as LV end-systolic volume and LV ejection fraction by RNA. Peak CK was also measured to further assess LV infarct size. The SPECT and RNA studies were completed between days 6 and 16 after the acute MI in 1,167 (40%) and 1,199 (41%) patients, respectively. The SPECT and RNA studies were analyzed by central core laboratories.

Statistical analysis. Baseline characteristics in patients with and without RV myocardial involvement and in patients with anterior MI were compared using the chi-square test for categorical variables and the *t* test for continuous variables. The incidences of death, pump failure and mechanical and electrical complications were compared after adjustment for age, gender and differences in baseline characteristics, using multivariable logistic regression. A

two-tailed *p* value <0.05 was considered as suggestive evidence and a two-tailed *p* value <0.01 was considered as persuasive evidence of a difference not due to chance alone. Differences in infarct size by SPECT and peak CK, and in LV ejection fraction and LV end-systolic volume, among the groups were analyzed by one-way analysis of variance. Multivariable logistic regression was used to identify predictors of six-month mortality in patients with inferior MI. **Meta-analysis.** Studies of RV myocardial involvement were identified from a computerized search of the MEDLINE data base between January 1966 and June 1999, reference lists and conference proceedings. Studies were selected by two independent reviewers, and disagreements were resolved by discussion. In order to be included, studies had to meet the following criteria: 1) include at least 50 patients with RV myocardial involvement; and 2) report clinical complications including mortality in patients with inferior MI with and without RV myocardial involvement. Six studies (including the present study) met our inclusion criteria. Data on clinical complications, death, cardiogenic shock, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) and advanced (second- or third-degree) atrioventricular block were extracted from each study and pooled using the Peto-Yusuf modification of the Mantel-Haenszel method under a fixed-effects model (5). Results are presented as odds ratios (OR) and 95% confidence intervals (CI), together with results of formal statistical testing for heterogeneity.

RESULTS

A total of 491 patients with RV myocardial involvement, 638 patients without RV myocardial involvement and 974 patients with anterior MI were studied. Ninety-six percent of patients received thrombolytic therapy.

Baseline characteristics. Table 1 summarizes the baseline characteristics for each of the MI groups. There was a lower proportion of males with RV myocardial involvement (72.4%) than those without RV myocardial involvement (80.4%) or anterior MI (79.1%) (*p* = 0.001). The proportion of smokers was higher in patients with (53.9%) and without (52.7%) RV myocardial involvement than in those with anterior MI (42%) (*p* = 0.001), whereas patients without RV myocardial involvement were more likely to have undergone previous coronary artery bypass graft surgery (5.3%) than those with RV myocardial involvement (2.7%) or anterior MI (2.8%) (*p* = 0.009). There was also a significant difference in the distribution of Killip class among the three groups, with a greater proportion of patients with anterior MI and RV myocardial involvement in Killip class 3 and 4 than patients without RV myocardial involvement. Patients with RV myocardial involvement had significantly lower systolic blood pressure (123 mm Hg) compared with patients without RV myocardial involvement (129.9 mm Hg) or anterior MI (134.4 mm Hg) (*p* = 0.001).

Table 1. Baseline Characteristics for Patients With Anterior Infarction and Inferior Infarction With and Without Right Ventricular Involvement

Characteristics	Anterior MI (n = 974)	Inferior MI		p Value
		RVMI (n = 491)	No RVMI (n = 638)	
Age (yr)	59.6	59.7	58.4	NS
Gender (% male)	79.1	72.4	80.4	0.001
Angina (%)	38.2	39.7	38.8	0.055
Myocardial infarction (%)	17.3	16.7	15.9	NS
Heart failure (%)	3.5	2.2	2.4	NS
Hypertension (%)	42.2	47.1	44.1	NS
Diabetes (%)	18.3	16.1	13.7	NS
Hyperlipidemia (%)	25.2	28.3	27.9	NS
CABG (%)	2.8	2.7	5.3	0.009
PTCA (%)	2.9	4.7	4.6	NS
Current smoker (%)	42.0	53.9	52.7	0.001
Thrombolytic therapy (%)	95.6	96.1	94.4	NS
Killip class (%)				
1	55.2	62.2	67.0	0.001
2	31.9	28.6	25.2	
3	6.8	4.1	3.5	
4	6.1	5.1	4.4	
Systolic BP (mm Hg)	134.4	123.0	129.9	0.001
Diastolic BP (mm Hg)	83.2	79.2	79.5	NS

BP = blood pressure; CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RVMI = right ventricular myocardial involvement.

Mortality, pump failure and mechanical complications. Mortality at hospital discharge, 35 days and 6 months was highest in patients with anterior MI (9.7%, 10.6% and 13.2%, respectively), intermediate in patients with RV myocardial involvement (7.1%, 7.5% and 8.9%, respectively) and lowest in patients without RV myocardial involvement (5.5%, 5.6% and 6.9%, respectively) (Table 2).

The incidences of in-hospital pump failure and mechanical complications are presented in Table 2. There was no significant difference in the incidence of left heart failure between patients with and those without RV myocardial involvement (OR 1.0, 95% CI 0.7 to 1.5), but the pooled incidence of left heart failure in these two groups was significantly lower than that in patients with anterior MI (11.6% vs. 17.7%, $p < 0.05$). Patients with RV myocardial involvement had a significantly higher incidence of hypotension requiring therapy compared with patients without RV myocardial involvement (OR 1.7, 95% CI 1.3 to 2.3) or anterior MI (OR 2.1, 95% CI 1.6 to 2.8). There was also a trend toward higher rates of cardiogenic shock in patients with RV myocardial involvement as compared with those without it (OR 1.3, 95% CI 0.8 to 2.1). The risk of cardiac rupture was intermediate in patients with RV myocardial involvement (0.8%) as compared with those with anterior MI (1.5%) and those without RV myocardial involvement

Table 2. Mortality and Other Complications During Hospital Period

	Anterior MI (%) (n = 971)	Inferior MI (%)		Odds Ratio (95% CI)		
		RVMI (n = 491)	No RVMI (n = 638)	RVMI vs. No RVMI	RVMI vs. Anterior MI	No RVMI vs. Anterior MI
Mortality						
In-hospital	9.7	7.1	5.5	1.3 (0.8-2.1)	0.7 (0.5-1.1)	0.5* (0.4-0.8)
At 35 days	10.6	7.5	5.6	1.4 (0.8-2.2)	0.7 (0.5-1.0)	0.5† (0.3-0.8)
At 6 months	13.2	8.9	6.9	1.3 (0.9-2.0)	0.6* (0.4-0.9)	0.5‡ (0.3-0.7)
Pump failure or mechanical complications						
Left heart failure	17.7	11.7	11.5	1.0 (0.7-1.5)	0.6* (0.4-0.8)	0.6† (0.4-0.8)
Cardiogenic shock	7.8	6.9	5.5	1.3 (0.8-2.1)	0.9 (0.6-1.3)	0.7 (0.4-1.0)
Cardiac rupture	1.5	0.8	0.3	2.6 (0.5-14.4)	0.5 (0.2-1.6)	0.2* (0.04-0.9)
Hypotension§	16.1	29.0	19.3	1.7‡ (1.3-2.3)	2.1‡ (1.6-2.8)	1.2 (1.0-1.6)
Electrical complications						
Atrial fibrillation	8.3	12.5	2.2	1.6 (1.1-2.4)	1.6 (1.1-2.3)	1.0 (0.9-1.4)
Ventricular fibrillation	5.0	8.4	2.7	3.3‡ (1.9-6.0)	1.7 (1.1-2.7)	0.5 (0.3-0.9)
Sustained VT¶	4.4	6.8	2.7	2.6† (1.4-4.8)	1.6 (1.0-2.5)	0.6 (0.3-1.0)
2° or 3° AV block	3.1	21.0	9.1	2.7‡ (1.9-3.7)	8.4 (5.5-12.8)	3.2‡ (2.0-5.0)

* $p < 0.01$. † $p < 0.001$. ‡ $p < 0.0001$. || $p < 0.05$. §Persistent hypotension requiring therapy. ¶ >120 beats/min for >30 s. AV = atrioventricular; CI = confidence interval; VT = ventricular fibrillation; other abbreviations as in Table 1.

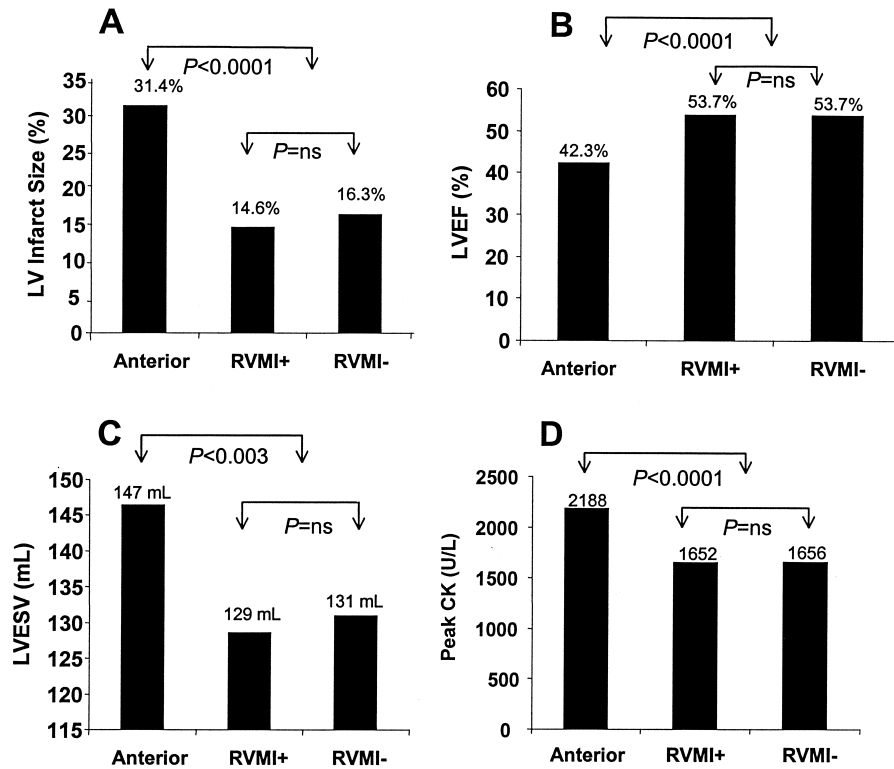


Figure 1. A, Left ventricular infarct size as measured by ^{99m}Tc -sestamibi SPECT perfusion imaging. B, Left ventricular ejection fraction (LVEF) as measured by RNA. C, Left ventricular end-systolic volume (LVESV) as measured by RNA. D, Peak CK. RVMI+ and RVMI- refer to patients with inferior MI with and without right ventricular myocardial involvement, respectively.

(0.3%). Cardiac rupture was significantly less common in patients without RV myocardial involvement as compared with those with anterior MI (OR 0.2, 95% CI 0.04 to 0.9). Reinfarction was not significantly different between patients with RV myocardial involvement (6.9%), those without RV myocardial involvement (7.7%) or those with anterior MI (5.5%). Similarly, there were no significant differences in postinfarction angina between the three groups (32.6%, 31.0% and 31.5%, respectively).

Electrical complications. The incidence of all serious arrhythmic complications was significantly higher in patients with RV myocardial involvement than in patients without RV myocardial involvement or those with anterior MI (Table 2). The risk of each of these arrhythmias was intermediate in patients with anterior MI and lowest in patients with inferior MI without RV myocardial involvement, except for 2° or 3° atrioventricular block, which was intermediate in patients without RV myocardial involvement and lowest in patients with anterior MI.

Infarct size, LV ejection fraction and LV end-systolic volume. Figure 1 displays the results of LV infarct size, as determined by SPECT and peak CK, and of LV function (LV ejection fraction and LV end-systolic volume), as determined by RNA. There was a consistent pattern for all four measures: LV infarct size was greatest and LV function was least in patients with anterior MI as compared with those with inferior MI with or without RV myocardial

involvement, but there was no difference in LV infarct size or LV function between patients with and those without RV myocardial involvement.

Predictors of poor outcome in inferior MI. The independent predictors of six-month mortality in patients with inferior MI are shown in Table 3. The presence of RV myocardial involvement was a powerful and independent predictor of six-month mortality. Other significant predictors included age, female gender, diabetes, angina and stroke. There appeared to an interaction between RV myocardial involvement and age. Treatment allocation (RheothRx or placebo) was not a significant predictor of mortality in our model.

Table 3. Independent Predictors of Six-Month Mortality in Inferior Myocardial Infarction*

Variable	Regression Coefficient	Standard Error	p Value
RVMI	6.9	1.74	0.0001
Age	0.12†	0.02	0.0001
Female gender	0.71	0.25	< 0.004
Diabetes	0.77	0.27	< 0.005
Angina	0.72	0.24	0.003
Stroke	1.0	0.41	0.01
Age·RVMI	0.10	0.03	0.0001

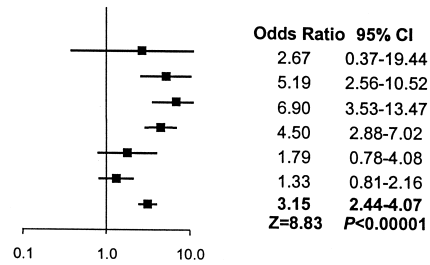
*Treatment (RheothRx or placebo) was not a significant predictor of mortality and was not included in the final model. †For a one-year increase.

RVMI = right ventricular myocardial involvement.

Prognostic Impact of Right Ventricular Infarction

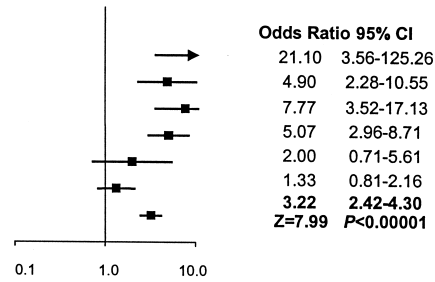
A. Mortality

STUDY	RVMI+	RVMI -
Berger, 1993	2/58	18/1052
Zehender, 1993	33/107	34/90
Bueno, 1997	36/77	11/109
Bueno, 1998	64/296	30/502
Zeymer, 1998	12/169	15/353
Mehta, 2001	35/491	35/638
TOTAL	184/1198	115/2747



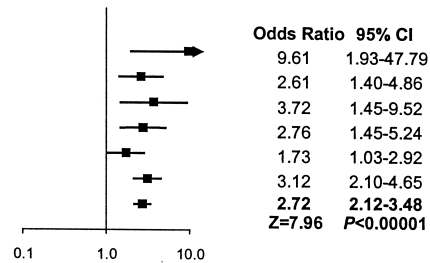
B. Cardiogenic Shock

STUDY	RVMI+	RVMI -
Berger, 1993	5/58	20/1052
Zehender, 1993	27/107	4/93
Bueno, 1997	25/77	5/109
Bueno, 1998	44/296	17/502
Zeymer, 1998	8/169	9/353
Mehta, 2001	35/491	35/638
TOTAL	143/1198	90/2747



C. Sustained VT or VF

STUDY	RVMI+	RVMI -
Berger, 1993	5/58	26/1052
Zehender, 1993	39/107	16/93
Bueno, 1997	14/77	6/109
Bueno, 1998	25/296	17/502
Zeymer, 1998	32/169	43/353
Mehta, 2001	75/491	34/638
TOTAL	190/1198	142/2747



D. Advanced AV Block

STUDY	RVMI+	RVMI -
Berger, 1993	11/58	113/1052
Zehender, 1993	18/107	4/93
Bueno, 1997	25/77	10/109
Bueno, 1998	75/296	34/502
Mehta, 2001	103/491	58/638
TOTAL	232/1029	219/2394

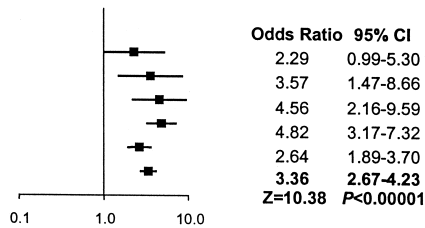


Figure 2. Meta-analysis of studies of right ventricular (RV) myocardial involvement/infarction. **A,** Mortality. **B,** Cardiogenic shock. **C,** Sustained VT or VF. **D,** Advanced atrioventricular block. The horizontal axis represents log odds ratio with 95% confidence interval (CI). RVMI+ and RVMI- refer to patients with inferior MI with and without right ventricular myocardial involvement, respectively. RVMI = right ventricular myocardial infarction.

Meta-analysis. Six studies (including ours), involving a total of 1,198 patients with RV myocardial involvement, met our inclusion criteria (6-10). Compared with patients who did not have RV myocardial involvement, those with RV myocardial involvement were at significantly increased risk of death (OR 3.2, 95% CI 2.4 to 4.1), cardiogenic shock (OR 3.2, 95% CI 2.4 to 4.3), sustained VT or VF (OR 2.7, 95% CI 2.1 to 3.5) and advanced atrioventricular block (OR 3.4, 95% CI 2.7 to 4.2), with relatively narrow CIs (Fig. 2). There was no difference in reinfarction rates between the two groups (OR 1.1, 95% CI 0.83 to 1.53).

DISCUSSION

To our knowledge, this is the single largest study to date that has evaluated the prognostic impact of RV myocardial involvement in patients with inferior MI. When combined with the results of previous smaller studies, the pooled clinical data provide clear evidence that patients with inferior MI who have RV myocardial involvement are at substantially increased risk of major complications, including death, cardiogenic shock and ventricular arrhythmias. Meanwhile, the lack of a difference in LV infarct size and function between these two groups, as demonstrated in our

study, indicates that the adverse prognosis in patients with RV myocardial involvement is not simply due to more extensive infarction of the LV; rather, it appears to be due directly to involvement of the RV.

Previous studies examining the prognostic impact of RV myocardial involvement in patients with inferior MI have involved small numbers of patients with very few outcome events (6-13). However, despite being the largest study to date, the point estimates in our study were also associated with wide confidence intervals, making it difficult to provide precise estimates of the increased risk of mortality and other complications associated with RV myocardial involvement. Therefore, to obtain a more reliable estimate of risk, we pooled the results from all of the studies performed to date in the form of a meta-analysis. Our meta-analysis clearly demonstrated that RV myocardial involvement was associated with a threefold increase in mortality, cardiogenic shock and serious arrhythmias, with narrow confidence limits.

The worse prognosis in patients with RV myocardial involvement may be related to the increased risk of life-threatening ventricular arrhythmias in these patients. Although atrioventricular block is a widely recognized complication of RV myocardial involvement (1,14), we also found clear increases in sustained VT and VF (2.7-fold) in these patients. This suggests that the RV may be more arrhythmogenic than the LV—a hypothesis that warrants further investigation.

Despite the higher risk of clinical complications in patients with inferior MI who also had RV myocardial involvement, our study demonstrated that LV infarct size and function were similar between patients with and those without RV myocardial involvement. Meanwhile, RV myocardial involvement remained an independent predictor of clinical outcome after adjustment for differences in baseline characteristics between patients with and those without RV myocardial involvement. These findings are consistent with those of a previous study of RV infarction in an elderly cohort, which demonstrated an independent association between RV myocardial involvement and in-hospital death, even after adjustment for LV ejection fraction (9). When we compared patients with RV myocardial involvement and patients with anterior MI, infarct size was significantly smaller and LV ejection fraction was higher, but patients with RV myocardial involvement still had significantly more atrial fibrillation, VT/VF, third-degree block and hypotension. Furthermore, these worse outcomes were not related to recurrent ischemia or reinfarction, which were similar among all of the groups.

Study limitations. Our study has several potential limitations. First, although it was our intent to obtain a lead V_{4R} in all patients with inferior MI, ~30% of patients presenting with inferior MI did not have lead V_{4R} analysis. However, there were no important differences in baseline characteristics between patients who did and those who did not have lead V_{4R} analysis, suggesting that our study group

was representative of the overall population of patients with inferior MI. Second, the diagnosis of RV myocardial involvement was based on ECG criteria alone, even though RV myocardial involvement is often considered to be a clinical syndrome in which hypotension and elevated right-sided pressure are required to make the diagnosis. However, ST segment elevation in lead V_{4R} has been shown in previous studies to be highly sensitive as well as specific for RV dysfunction in acute inferior MI (7,15-17). Finally, selection bias is a potential limitation of this study because of the nonconsecutive recruitment of patients. However, large differences in outcomes between patients with and those without RV myocardial involvement were observed even within the constraints of a randomized trial data base and may be expected to be even larger in everyday clinical practice.

Clinical implications. Our study suggests that right-sided precordial leads should be performed in all patients presenting with acute inferior MI, rather than only in patients thought to have large infarctions. The routine adoption of this approach will facilitate the early identification of patients with RV myocardial involvement who are at high risk of life-threatening complications and who may warrant more aggressive treatment. Recent data suggest that successful reperfusion with primary coronary angioplasty can achieve dramatic improvements in RV performance and improved clinical outcomes in patients with RV myocardial involvement (18). However, whether this strategy is superior to thrombolytic therapy in this patient group remains to be demonstrated and awaits evaluation within the context of a randomized trial.

Reprint requests and correspondence: Dr. Shamir Mehta, Division of Cardiology, McMaster University Medical Center, 1200 Main Street, West HSC-345, Hamilton, Ontario, Canada L8N3Z5. E-mail: smehta@fhs.mcmaster.ca.

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