I mmediately after acute infarction, the region of the myo-
cardium ceases to contract, and over the next 72 hours, the
infarct zone stretches and thins, a process known as infarct
expansion. This regional left ventricular wall thinning and
failure to contract perturb the normally uniform distribution
of the stress/strain relationship that preserves cardiac archi-
tecture and function. Simultaneous with these early biome-
chanical changes, myocyte necrosis releases a number of
cytokines that, together with the local increase in the
regional myocardial deformation, cause stretch activation
of a portfolio of matrix metalloproteinases that initiate
myocardial repair.

The stability of myocardial repair after acute myocardial
infarction is determined by the balance between the distend-
ing forces from ventricular dilatation resulting from infarct
expansion and the restraining forces from deposition of a
viscoelastic collagen scaffold by the extracellular matrix that
increases the tensile strength of the scar. The dynamic
equilibrium between collagen degradation and collagen dep-
osition is modulated by a number of activated cytokines and
neurohormones that normally result in buttressing the infarct
and adjacent border zones, preventing progressive remodel-
ing to heart failure.

Changes in the composition of the myocardium in terms of
increased collagen content during and after repair of the
infarct zone in forming a fibrous tissue scar alter the material
properties of the myocardium after myocardial infarction and
confers on the heart increased myocardial and chamber stiff-
ness. These alterations in left ventricular composition, archi-
tecture, and chamber/myocardial stiffness affect left ventricu-
lar filling dynamics, the rate of detachment of cross-linking,
and sequestration of cytosolic calcium by the sarcoplasmic
reticulum, all of which affect diastolic function as much as
systolic function. However, most studies of the predictors of
clinical outcome after myocardial infarction have focused
almost exclusively on ejection-phase indexes of systolic
function. Nevertheless, mitral regurgitation, left ventricular hypertrophy (left
ventricular mass), frequent ventricular arrhythmias, and pro-
gressive ventricular remodeling.1–4 In contrast, there is a
remarkable absence of any measure of left ventricular dia-
stolic function that predicts clinical outcome after myocardial
infarction. The diastolic phase of the cardiac cycle has been
overlooked as a prognostic indicator despite the important
relationship between left ventricular filling and stroke volume
described by Starling’s law of the heart. The reason for this
absence is due in part to the fact that until relatively recently
the significance of diastolic left ventricular dysfunction was
not appreciated. Although diastolic dysfunction was observed
to often precede the onset of systolic dysfunction in ischemic
heart disease, diastolic heart failure with preserved ejection
fraction (>50%) was believed to be relatively uncommon and
was regarded as relatively benign. Furthermore, there was no
reliable and reproducible measure of diastolic function that
was independent of age, heart rate, and left ventricular
loading conditions that was predictive of clinical outcome
after myocardial infarction. The wide spectrum of abnormal-
ancies of diastolic filling is based largely on transmitral and
pulmonary vein blood flow velocity profiles recorded by
Doppler echocardiography and myocardial velocities rec-
corded with Doppler tissue imaging during the passive rapid
filling phase and atriosystolic contraction. For practical pur-
poses, the left ventricular filling patterns are divided into 4
different stages.5–9 The first stage, abnormal left ventricular
filling pattern, describes mild diastolic dysfunction caused by
abnormal myocardial relaxation that is reversible. In the
second stage, moderate diastolic dysfunction, the ventricular
filling pattern is pseudonormal and reversible. Stages 3 and 4
describe severe diastolic dysfunction characterized by a
restrictive filling pattern typified by an elevated E-wave
velocity, a truncated deceleration time of <140 ms, and an
increased E/A peak velocity.5–9 Stage 3 is still reversible; stage
4 is irreversible. A few small studies have indicated that
restrictive filling, the most advanced impairment of left
ventricular filling, predicts clinical outcome,10,11 but other
studies have failed to demonstrate the predictive value of
restrictive diastolic filling.12,13 Hitherto, no previous study
has investigated the importance of a restrictive pattern of left
ventricular filling in predicting mortality after infarction
independently of left ventricular size, ejection fraction, and
Killip class.

The true importance of diastolic function has emerged over
the last decade because currently between one third and one
half of all patients presenting with clinical heart failure have
severe diastolic dysfunction and preserved systolic func-
tion.14 This combination has been variously called diastolic heart failure or heart failure with preserved systolic function as evidenced by an ejection fraction of ≥50%.14,15

Whalley et al.16 on behalf of the Meta-Analysis Research Group in Echocardiography Acute Myocardial Infarction (MeRGE AMI) investigators, report in this issue of Circulation the results of a meta-analysis of 12 prospective postinfarction clinical trials in which restrictive left ventricular filling was estimated to occur in ≈20% of a large cohort of 3739 survivors of acute myocardial infarction. No attempt was made by the authors to differentiate between patients with stage 3 and stage 4 diastolic dysfunction, that is, to determine whether the restrictive filling pattern was reversible. The prespecified aims were to determine the difference in mortality between patients with nonrestrictive and restrictive filling pattern and, in particular, to determine whether the restrictive filling pattern predicted mortality independently of end-systolic left ventricular volume index, ejection fraction, and Killip class after infarction.

The study population comprised a large number (3396) of postinfarction patients followed up for ≈4 years. Patients with atrial fibrillation and technically limited Doppler echocardiograms were excluded.

Restrictive filling was predefined somewhat imprecisely as a “high” E/A ratio or a deceleration time of the E wave of <140 ms. In addition, the precise timing of the Doppler transmitral flow velocity acquisition relative to the time of infarction is not stated in this study or in another report17 other than that it was obtained within the first 2 weeks after infarction. The timing of the echocardiography is important in that left ventricular chamber and myocardial stiffness may fluctuate before and after the infarct repair process is completed.14 Patients were dichotomized at the time of their Doppler echocardiogram as to whether they had restrictive left ventricular diastolic filling or nonrestrictive filling patterns. Left ventricular volumes indexed to body surface area and ejection fractions were estimated. Comparison of the patient population with restrictive filling and the population without restrictive filling revealed some major differences in baseline demographics with regard to risk factor profiles and left ventricular morphology and function. The restrictive filling group had a greater prevalence of diabetes, hyperlipidemia, and anterior myocardial infarctions. In addition, this group had significantly larger left ventricular volumes, lower ejection fractions, and higher Killip class than the group with nonrestrictive left ventricular filling patterns. Doppler peak E/A velocity ratio and deceleration time were both statistically significantly different by definition between the 2 patient groups. The important major finding in this study is the almost 3-fold difference in the 90% survival times: 39 days (29%) in the group with the restrictive left ventricular filling pattern versus 802 days (11%) in those with nonrestrictive filling pattern. Throughout the 4-year follow-up available in this meta-analysis, a restrictive left ventricular filling pattern was associated with a significantly reduced survival compared with a nonrestrictive filling pattern.

Targeted subgroup analysis was performed to determine whether the predictive power of restrictive diastolic filling pattern for mortality was independent of ejection fraction. Quartile analysis based on left ventricular ejection fraction showed that patients in the lowest quartile were older and had larger left ventricular volumes and a higher incidence of both anterior infarction and Killip class III/IV. The prevalence of restrictive filling and mortality varied inversely with ejection fraction from quartile 1 through quartile 4. However, the relationship between restrictive filling pattern and mortality within each quartile was maintained. The 90% survival times were reduced in patients with restrictive filling patterns compared with nonrestrictive filling in each quartile, and an important finding was that no interaction was found between ejection fraction and restrictive filling pattern for predicting mortality after infarction.

Estimations of left ventricular end-systolic volume index were available in almost half of the study population. When patients were dichotomized using the median end-systolic volume index of 35 mL/m², there were significantly more patients with restrictive filling pattern with end-systolic volume indexes greater than the median (36% versus 15%) than below the median end-systolic volume index. However, regardless of left ventricular volume index, a restrictive left ventricular filling pattern remained a significant predictor for mortality.

Killip class was determined in half the patients (51%). Of the patients who had heart failure diagnosed in hospital, 61% had a restrictive filling pattern, whereas heart failure was present in only 30% of patients with nonrestrictive filling. There was a stepwise increase in restrictive filling with increasing Killip class, but there was no interaction between restrictive filling pattern and Killip class in predicting clinical outcome after infarction. Multivariate analysis showed no significant interaction with age and sex for risk of death associated with restrictive left ventricular filling. However, when clinical data such as diabetes, β-adrenergic receptor blockers, and angiotensin-converting enzyme inhibitors were added to the statistical model, restrictive filling pattern remained a robust predictor of clinical outcome. Diabetes reduced mortality but angiotensin-converting enzyme inhibitors improved mortality.

This meta-analysis of 12 prospective clinical trials of survivors of acute myocardial infarction, designed to determine whether simple, universally available Doppler echocardiographic measurements of left ventricular diastolic function predict clinical outcome, provides important and thought-provoking findings. Despite no data on the impact of the precise timing of the Doppler echocardiogram, the different baseline demographics, and the potential influence of discordant postinfarction pharmacotherapies between the 2 groups, 2 indelibly clear messages emerge. The first message is that a restrictive left ventricular filling pattern predicts clinical outcome after infarction even in the presence of a normal ejection fraction. Restrictive filling is associated with a 3-fold increase in risk of death. A restrictive filling pattern provides incremental prognostic information over and above that of left ventricular volumes and Killip class. The second message is that left ventricular filling profiles should be evaluated in every patient after myocardial infarction to stratify patients at increased risk of death. The tools used to measure diastolic function in this study were simple and typify the strategy used.
for clinical trials. Today, diastolic function can be dissected more completely into its components by measurements of propagation velocity, automated tissue tracking, strain, strain rate, and Doppler tissue imaging so that the effects of left ventricular loading conditions and abnormal relaxation can be resolved.6,9

Disclosures

None.

References


Quest for Diastolic Prognostic Indicators of Clinical Outcome After Acute Myocardial Infarction
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Circulation. 2008;117:2570-2572
doi: 10.1161/CIRCULATIONAHA.108.772483

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