Prognostic Importance of Diastolic Function and Filling Pressure in Patients With Acute Myocardial Infarction

Jacob E. Møller, MD, PhD; Patricia A. Pellikka, MD; Graham S. Hillis, MBChB, PhD; Jae K. Oh, MD

A
cute myocardial infarction (AMI) is characterized by re-
gegional myocardial damage that may lead to systolic and
diastolic dysfunction with a subsequent risk of left ventricular
(LV) remodeling, local and systemic neurohormonal activation,
and vascular dysfunction. The pathophysiology and prognosis
of LV systolic dysfunction after AMI have been the focus of
research for several decades. Insights from these studies have led
to several therapeutic interventions that improve outcome. In
addition to depressed systolic function, clinical or radiographic
evidence of heart failure is a consistent and powerful predictor of
outcome in patients after AMI.1 Pulmonary congestion after
AMI is a common finding and a consistent and powerful predictor of
outcome in patients after AMI.1

The pathophysiological mechanism for this is incompletely
understood but may involve impaired active relaxation of the
myocardium and increased LV chamber stiffness and hence
abnormalities in diastolic function. If these are to be determined
directly, cardiac catheterization with assessment of pressure-
volume relationships with the use of high-fidelity micromanom-
eter catheters is required. This highly specialized approach is not
suitable for daily clinical practice. Likewise, although direct
measurements of right heart or LV end-diastolic pressure are
important predictors of adverse outcome after AMI in selected
populations,3,4 the risk of complications precludes routine use of
indwelling catheters in all patients. There has therefore been
considerable interest in using noninvasive estimates of diastolic
function, particularly Doppler echocardiographic assessment of
LV filling dynamics and, more recently, the volume of the left
atrium (LA), to predict outcome in patients with AMI.

The objective of this review is to summarize the current under-
standing of abnormal LV filling in the early phase after AMI with
focus on the complementary prognostic information that may be
gained by assessment of LV filling dynamics and LA volume with
the use of 2-dimensional and Doppler echocardiography.

Doppler Echocardiographic Assessment of
Diastolic Function

After an AMI, myocardial ischemia, cell necrosis, microvascular
dysfunction, and regional wall motion abnormalities will influ-
ce the rate of active relaxation. In addition, interstitial edema,
fibrocellular infiltration, and scar formation will directly affect
LV chamber stiffness. Thus, abnormalities in LV filling are
common in this setting.

Spectral Pulsed-Wave
Doppler Echocardiography

The pulsed-wave Doppler technique allows assessment of flow
velocities (<2 m/s) at a distinct spatial position, making the
technique suitable for assessment of changes in inflow velocities
across the mitral valve during diastole. With mitral valve
opening, the early inflow velocity will be determined largely by
ventricular suction and the pressure gradient between the LA and
LV.5–7 This is followed by a steady decrease in inflow velocity,
with a normal duration of 140 to 240 ms (early mitral deceler-
ation time [DT]) (Figure 1). After a period of diastasis, atrial
contraction will cause a new increase in inflow velocity less than
that of the early inflow; thus, the ratio of early to atrial inflow
velocities (E/A ratio) will usually be 1 to 1.5.

If active relaxation is impaired, the early mitral inflow
velocity will decrease, increasing the atrial contribution to
filling, resulting in a reversal of the E/A ratio and a prolonged
DT. This “impaired relaxation” pattern, indicative of grade 1
diastolic dysfunction, is usually associated with normal LV
filling pressure (Figure 2). With worsening of diastolic
dysfunction, LA pressure increases, and the gradient between
the LA and LV at mitral valve opening increases; hence, the
velocity of early inflow will increase even though relaxation
is impaired. Because of rapid equilibration, early ventricular
filling is terminated abruptly, causing a shortening of the time
period during which early filling occurs; hence, DT returns to
normal. Therefore, the combination of delayed relaxation and
elevated LA pressure may create an apparently normal
transmitral inflow pattern that has been termed pseudonormal
(grade 2 diastolic dysfunction) (Figure 1). With further
deterioration, early filling will terminate abruptly because of
the increase in LV stiffness. The DT will be abnormally short
and the E/A ratio will be high, a pattern termed restrictive
(grade 3 diastolic dysfunction) (Figure 2). The restrictive
filling pattern can be subdivided further as reversible, if
preload reduction, accomplished either by treatment or by the
Valsalva maneuver, causes reversal of the filling pattern to
the nonrestrictive pattern, or irreversible, if preload reduction
causes no reversal of the filling pattern.5,6 In patients with
previous AMI, short DT (<140 ms) is associated with
elevated LV filling pressures,8,9 even in the presence of atrial
fibrillation10,11 and irrespective of the severity of mitral

From the Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (J.E.M.); the Division of Cardiovascular Diseases, Mayo Clinic, Rochester,
Minn (P.A.P., J.K.O.); and Department of Cardiology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK (G.S.H.).

Correspondence to Patricia A. Pellikka, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail pellikka.patricia@mayo.edu

(Circulation. 2006;114:438-444.)

© 2006 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/CIRCULATIONAHA.105.601005

438
regurgitation.\textsuperscript{12} In contrast, DT >140 ms, especially in patients with preserved LV systolic function, correlates poorly with filling pressures.\textsuperscript{9,13}

Although transmitral filling patterns are fundamental to the assessment of LV diastolic function, they have several limitations. They may change rapidly with variations in preload.\textsuperscript{14–17} Pseudonormalization of the inflow pattern despite moderate elevation of filling pressures is a further major shortcoming. To overcome this, less load-dependent indices of LV filling can be used, usually in combination with transmitral parameters. These may include assessment of the pulmonary venous flow pattern. This, however, is difficult to obtain in all patients\textsuperscript{19} and is greatly affected by heart rhythm. Thus, other techniques have been developed. The most extensively validated of these are the determination of blood flow propagation within the LV with the use of color M-mode and tissue Doppler assessment of mitral annulus motion during diastole.

**Figure 1.** Spectral pulsed-wave (PW) Doppler recording of mitral inflow, tissue Doppler recording of septal mitral annular longitudinal motion, color M-mode recording of LV inflow, and 2-dimensional image for assessment of LA volume (only shown in apical 4-chamber view). A, Images were obtained in a 48-year-old healthy subject; mitral DT 185 ms, peak E-wave velocity 88 cm/s, septal e’ velocity 16 cm/s, E/e’ ratio 5.5, flow Vp 78 cm/s, LA volume index 26 mL/m\textsuperscript{2}. B, Images were obtained in a 67-year-old man 1 day after ST-segment elevation AMI treated with primary angioplasty (stenting of left anterior descending coronary artery) demonstrating a pseudonormal LV filling pattern; DT 190 ms, E-wave velocity 85 cm/s, septal e’ 5 cm/s, E/e’ ratio 17, Vp 37 cm/s, LA volume index 55 mL/m\textsuperscript{2}.

**Figure 2.** Grading of LV filling. PW indicates pulsed wave.
Color M-Mode Doppler Echocardiography

The color M-mode Doppler technique, performed in the apical 4-chamber view, reflects the distribution of blood velocities along a vertical line from the mitral plane to the apex of the LV. Color M-mode therefore provides spatiotemporal information on the propagation of blood into the LV (Figure 1). The slope of this early surge of blood into the LV has been termed flow propagation velocity ($V_p$), which is slowed when relaxation is impaired and, in contrast to the mitral E wave, remains reduced when LA pressure increases. $V_p$ is also affected by LV geometry, intraventricular pressure gradients, and synchrony of wall relaxation.20–22 Several studies have demonstrated a negative correlation between $V_p$ and invasive measures of LV relaxation during myocardial ischemia and during both blockade and stimulation of β-adrenergic receptors.14,20,21 Under physiological conditions, $V_p$ has been demonstrated to be relatively preload independent.14,23 Based on this, $V_p$ has been used in combination with peak mitral E-wave velocity to assess filling pressures and has proven useful in detecting a pseudonormalized LV filling pattern.24–28 The ratio of mitral E to $V_p$ allows estimation of filling pressure during sinus rhythm or atrial fibrillation; E/$V_p$ ratio >1.5 is suggestive of increased (>15 mm Hg) pulmonary capillary wedge pressure.27,28 Although useful in many situations, the assessment of LV filling with flow propagation has limitations. In ventricles with severe hypertrophy, $V_p$ may appear normal because of enhanced intraventricular gradients despite delayed relaxation.29 In addition, several different methods for acquisition and analysis of color M-mode recordings have been used. In the majority of more recent studies, the method proposed by Garcia et al30 has been adopted (Figure 1). According to this method, the M-mode cursor is positioned in the center of LV inflow, avoiding boundary regions. $V_p$ is measured as the first aliasing velocity (45 cm/s) from the mitral annulus in early diastole to 4 cm distally into the LV cavity. In patients with a low mitral E-wave velocity, baseline shift is adjusted to alias at ~75% of the E-wave velocity. Even when this method is used, the interobserver variability may be as high as 10% to 20%, with the greatest variability for high (normal) values of $V_p$.

Spectral Pulsed-Wave Tissue Doppler Echocardiography

The motion of myocardium during the cardiac cycle can be displayed as a spectral pulsed-wave Doppler image, in which the signal will reflect the movement of myocardium parallel with the Doppler cursor. Because the apex of the LV is relatively fixed throughout the cardiac cycle and the motion of the LV base is nearly parallel with the long axis, assessment of the movement of the basal LV segments reflects the longitudinal vector of contraction and relaxation. Early diastolic mitral annulus velocity ($e’$) is a useful indicator of LV relaxation. Invasive studies have demonstrated that $e’$ correlates inversely with invasive indices of relaxation.17,18,31 In the presence of low (<0.1 m/s) velocities, $e’$ is less affected by changes in preload17,31 and may be used to identify pseudonormal LV filling.17,32,33 Using the ratio of peak mitral E-wave velocity to early mitral annulus velocity (E/$e’$), numerous studies have demonstrated a good approximation of LV filling pressures. This relationship has been validated in the presence of atrial fibrillation,28 sinus tachycardia,34 preserved or depressed LV systolic function,38 secondary mitral regurgitation,35 and LV hypertrophy.36 Ommen et al36 demonstrated that E/$e’$ >15 accurately detects elevated filling pressures, and E/$e’$ <8 accurately detects normal LV filling pressures. However, because the Doppler method tracks the velocity of movement, tissue Doppler cannot separate active contraction from passive tethering. Annular velocities vary depending on the location sampled, with the velocity of the lateral annulus usually higher than that of the septal annulus. This has led to controversy about which site should be used. Local myocardial damage may affect the mitral annular velocity, which may be a theoretical disadvantage of this measurement in AMI.

Tissue Doppler or Color M-Mode for Assessment of LV Filling?

Although different in methodology, both tissue Doppler and color M-mode are relatively preload insensitive, allow estimation of filling pressures with reasonable accuracy, and facilitate identification of the pseudonormal LV filling pattern. In patients with small LV cavities due to hypertrophy, tissue Doppler is preferred because of pseudonormalization of $V_p$. Although $V_p$ has a good reproducibility for distinguishing normal from abnormal,37 the reproducibility of $e’$ is superior. In assessment of filling pressures and detection of pseudonormal LV filling, most studies32,33,38–40 but not all41 that have compared the techniques have favored E/$e’$. Thus, the better reproducibility and lesser dependence on LV geometry make tissue Doppler echocardiography $e’$ measurement the preferred technique.

LA Volume as a Marker of Diastolic Dysfunction

The LA acts as a conduit between the pulmonary vascular bed and the LV, receiving blood from the pulmonary veins and conveying it to the LV through passive and active filling. In addition, the atrium acts as an efficient volume sensor, releasing natriuretic peptides and other neurohormones to the circulation as a consequence of increased atrial wall stress. After opening of the mitral valve, the LA and LV diastolic pressures will rapidly equalize, and emptying of the LA will be determined largely by LV filling dynamics.42,43 Thus, when the LA empties against a noncompliant LV and/or there is an increase in LV end-diastolic pressure, LA pressure will rise. This is poorly tolerated by the thin wall of the LA, and subsequent dilation will occur.43 Chronic LA pressure overload will cause reduced myocardial energy production, alterations in contractile proteins, and myocyte atrophy, which eventually will cause LA wall fibrosis. Thus, with chronic distension there is little elastic recoil in the LA, and a chronically enlarged atrium will be relatively unaffected by transient changes in LA pressure.43,44 Because of this relative insensitivity to transient changes in filling pressures, LA size can be considered a biomarker of sustained elevations in LV filling pressures.

With the use of echocardiography, LA size has traditionally been estimated with M-mode measurements obtained in the parasternal long-axis view, reflecting the anteroposterior dimension of the LA. However, the LA does not dilate symmetrically because of physical restraint.45 Thus, with expansion of the LA, the anteroposterior dimension by M-mode will underestimate the true volume.45 With the use of planimetry performed in the apical window, the LA volume may be assessed by either single
or biplane methods, with high reproducibility and good correlation with volumetric assessment with the use of magnetic resonance and 3D-cine computed ventriculography. Compared with magnetic resonance, echocardiographic measurement of LA volume results in a slight underestimation. This is less important when echocardiographic reference ranges are used. These are indexed to the body surface area of the patients, and the normal upper limit (mean +2 SD) of echocardiographically determined LA volume index has been determined to be 32 mL/m².

Relation Between LV Filling Pattern/LA Size and Prognosis After AMI

The prognostic importance of a restrictive filling pattern after AMI was initially reported by Oh et al in 1992. In a cohort of 62 patients, a restrictive filling pattern was associated with a high occurrence of in-hospital congestive heart failure. This was confirmed by Poulsen et al in an age-selected population with a first AMI in which Doppler echocardiography was performed within 1 hour of hospital admission. In 1997, Nijland et al reported in a study of 95 patients with first AMI that DT <140 ms was associated with a 22% survival rate at 3 years compared with 100% in the nonrestrictive group. Although the study was limited by a small number of deaths (n=8), this finding has subsequently been confirmed in several studies. Although these studies, patients with a restrictive filling pattern have been characterized by higher age, more advanced LV systolic dysfunction, and a high risk of in-hospital heart failure. A restrictive filling pattern seems to have the same prognostic importance in ST- and non–ST-segment elevation AMI and in patients treated with thrombolysis or primary angioplasty. Although the results of those studies have been strikingly similar, many have been limited by small populations and few events. However, in 799 patients with assessment of LV filling within 6 days of AMI, DT <140 ms was a predictor of all-cause mortality, with a hazard ratio of 2.1 (95% CI, 1.5 to 3.1), after adjustment for various clinical variables including in-hospital heart failure and LV systolic function. This has recently been replicated in 2 other large studies. These studies of >2500 patients have shown that an abnormally short DT is an independent predictor of adverse outcome after AMI and is incremental to conventional indicators of poor outcome such as age, Killip class, enzymatic infarct size, ejection fraction, wall motion score index, and end-systolic volume. However, a large study among 520 patients with ST-segment elevation AMI treated with fibrinolysis enrolled in the ATTEnuation by Adenosine of Cardiac Complications (ATTACC) study failed to find an independent prognostic importance of restrictive filling. Restrictive filling was defined by either DT <140 ms or E/e’ could prove useful. This was recently demonstrated in a retrospective study of 250 patients with AMI; an increased (>15) E/e’ ratio was found to be an important predictor of all-cause mortality incremental to LVEF, age, and a restrictive filling transmitral filling pattern. Importantly, E/e’ allowed risk stratification among patients with preserved as well as depressed LV systolic function. This supports the finding of an adverse outcome in patients with pseudonormal filling (moderate increase in filling pressures) despite preserved LV systolic function and concurs with the results of studies in which the E/N ratio was used. When LV filling is assessed with the use of transmitral, color M-mode, and tissue Doppler echocardiography, an instantaneous assessment of filling dynamics will be obtained. During the acute phase of AMI, intravenous administration of nitroglycerin and β-blockers, resolving myocardial ischemia, early infarct healing, changes in LV geometry, and a variety of other factors will affect LV loading conditions and filling patterns. Therefore, a more stable indicator reflecting the duration and severity of abnormal LV filling would be desirable. LA volume has been proposed as such an indicator.

Relation Between Noninvasively Estimated Filling Pressure and Prognosis After AMI

In the absence of direct measurements of filling pressures, noninvasive estimation of filling pressures with the use of E/N or E/e’ could prove useful. This was recently demonstrated in a retrospective study of 250 patients with AMI; an increased (>15) E/e’ ratio was found to be an important predictor of all-cause mortality incremental to LVEF, age, and a restrictive filling transmitral filling pattern. Importantly, E/e’ allowed risk stratification among patients with preserved as well as depressed LV systolic function. This supports the finding of an adverse outcome in patients with pseudonormal filling (moderate increase in filling pressures) despite preserved LV systolic function and concurs with the results of studies in which the E/N ratio was used. When LV filling is assessed with the use of transmitral, color M-mode, and tissue Doppler echocardiography, an instantaneous assessment of filling dynamics will be obtained. During the acute phase of AMI, intravenous administration of nitroglycerin and β-blockers, resolving myocardial ischemia, early infarct healing, changes in LV geometry, and a variety of other factors will affect LV loading conditions and filling patterns. Therefore, a more stable indicator reflecting the duration and severity of abnormal LV filling would be desirable. LA volume has been proposed as such an indicator.

Relation Between LA Size and Prognosis After AMI

Two recent studies have investigated the relation between LA dilatation and all-cause mortality after AMI. In a retrospective design including 314 patients, an increase >32 mL/m² in LA volume index was associated with a high
all-cause mortality rate. In multivariate analysis, LA volume, Killip class, and a restrictive transmural filling pattern were independent predictors of death, whereas LVEF or wall motion score index did not provide any additional prognostic information. A striking finding was that among patients with LVEF <40%, the LA appeared normal in size in one third of patients (27 of 82). One death occurred in this group as opposed to 22 deaths among 55 patients with LVEF <40% and LA enlargement. In addition, the prognostic importance of LA volume was unrelated to the presence and severity of mitral regurgitation and atrial fibrillation. This finding has subsequently been confirmed by Beinart et al in a prospective study of 395 patients with AMI in which multivariable analysis also identified restrictive filling, Killip class, and LA volume as independent predictors of adverse outcome.

Why Do Patients With Abnormal LV Filling/Enlarged LA Have a Poor Prognosis?
Consistently, irrespective of the method of assessment, it is evident that if there are direct or indirect signs of increased LV filling pressures, the risk of death is increased. Although the prevalence and severity of filling abnormalities are associated with the severity of systolic dysfunction, a considerable proportion of patients present with Doppler signs of elevated filling pressures despite only mildly reduced LVEF. The reason why these patients poorly tolerate what appears to be a relatively small myocardial injury is incompletely understood. These patients are older and more likely have a history of hypertension and diabetes compared with patients with no signs of elevated filling pressures. They also have evidence of more generalized overt atherosclerotic disease.

The progression of cardiovascular disease can be regarded as a continuum of events in which the presence of risk factors such as hypertension, diabetes, and dyslipidemia predisposes to the development of atherosclerosis, LV hypertrophy, and eventually overt coronary artery disease and cardiac failure. LA volume has been shown to correlate positively with age and clinical cardiovascular risk score and negatively with LVEF. We speculate that patients with increased LV filling pressures immediately after AMI have an increased burden of risk and poorly tolerate an acute loss of even relatively small amounts of myocardium. This is supported by the fact that a considerable number of patients, even when evaluated during the first 24 hours of AMI, present with LA enlargement. Based on the physiology of the LA, it would not be anticipated that acute elevation of filling pressures within hours can cause LA dilatation. This suggests that even before AMI, some patients had abnormal LV filling and possibly abnormalities in chamber stiffness and active relaxation with subsequent poor adaptation to the hemodynamic changes during acute myocardial ischemia.

LV pressure overload will cause myocyte stretch, increased wall stress, poorer subendocardial perfusion, and reduced energy production. These in turn are associated with neurohumoral activation and ventricular remodeling. Although the remodeling process will initially restore stroke volume and systemic hemodynamics, continuing dilation will have a detrimental effect on long-term LV function and survival. Previous studies of unsel ected patients with AMI, patients with preserved systolic function, and patients with ST-segment elevation AMI treated with fibrinolysis or successful primary angioplasty have demonstrated that a restrictive filling pattern in the early postinfarction phase predicts LV remodeling, defined as a dilatation (>20%) of the LV end-diastolic volume. This provides an important link to long-term prognosis.

How to Treat Abnormal LV Filling
A major unresolved question is how to manage optimally patients with abnormal LV filling especially if LVEF is normal or only mildly reduced. To date, no interventional trial has been undertaken with hard end points in which patient selection has been based on abnormalities in LV filling. However, assessment of the inflow pattern and E/e' ratio may provide important information on the hemodynamic status and guide the use of vasodilators and diuretics. In addition, previous randomized data have demonstrated that attenuation of the renin-angiotensin-aldosterone system with captopril in patients with mildly to moderately depressed LVEF after AMI is associated with a major improvement in central hemodynamics (LV end-diastolic and pulmonary artery pressure), whereas the improvement in LVEF is modest. Likewise, small studies have demonstrated improvements in LV filling on intervention with β-blockers after AMI, which was associated with improved exercise capacity. However, although this reduction in LV filling pressure would be anticipated to improve functional status, it is not known whether this is associated with a better outcome.

Summary
Doppler echocardiographic assessment of hemodynamics in the acute setting of AMI provides independent noninvasive prognostic information. This is particularly true in the subgroup of patients who have evidence of elevated LV filling pressures despite relatively preserved systolic function. Although ventricular remodeling and hyperactivity of the renin-angiotensin-aldosterone system most likely contribute to the excess mortality in these patients, further work is required to increase our understanding of the pathophysiology. As our knowledge expands, it is likely that this will lead to new opportunities to modify the excess risk and improve patient outcome.

Disclosures
None.

References
4. García-Rubira JC, Molano F, Espina A, Calvo R, Gonzalez-Valday M, García-Martínez JT, Cruz JM. Abnormal filling pattern of the left ven-
tricle and outcome in acute myocardial infarction. *Int J Cardiol*. 1997; 61:143–149.


17. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD, Lee YW. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol*. 1997;30:474–480.


41. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and


Key Words: diastole echocardiography heart diseases ischemia myocardial infarction
Prognostic Importance of Diastolic Function and Filling Pressure in Patients With Acute Myocardial Infarction

Jacob E. Møller, Patricia A. Pellikka, Graham S. Hillis and Jae K. Oh

_Circulation._ 2006;114:438-444
doi: 10.1161/CIRCULATIONAHA.105.601005

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/5/438

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the _Permissions and Rights Question and Answer_ document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/