Echo-Doppler evaluation of left ventricular diastolic dysfunction during acute myocardial infarction: methodological, clinical and prognostic implications

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Left ventricular (LV) diastolic dysfunction has been reported in the subacute and late phase after myocardial infarction and it is becoming increasingly clear that abnormalities of diastolic function during acute myocardial infarction (AMI) have a major role in affecting the prognosis. However, until recent years the study of patients with diastolic dysfunction has suffered from the substantial difficulties inherent in diagnosing, measuring, quantitating and in following it over time. Moreover, the complexity of events encompassed by diastole, which are often difficult to control in the clinical arena, and the lack of data available to guide therapy, have hampered the widespread application of diastology in the clinical setting of AMI. The advent of Doppler echocardiography and its complementary techniques have provided a bedside tool which yields reliable and useful measures of diastolic performance during AMI, placing such an assessment well within the grasp of every clinical echocardiographic laboratory. Determination of the pattern of LV filling by Doppler echocardiography provides important information about LV diastolic function in AMI patients. Clinical data gathered so far demonstrate that Doppler-derived LV filling, specifically the restrictive filling pattern, is a powerful independent predictor of late LV dilation and, most importantly, of cardiac death in patients with AMI and clearly indicate the need for evaluating and monitoring LV diastolic function in these patients. Large scale studies, utilizing simple and easy to measure Doppler indexes of LV filling are needed to assess the efficacy of medical therapy in patients with acute LV diastolic dysfunction during AMI.

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Left ventricular (LV) systolic function after acute myocardial infarction (AMI) has been extensively studied, and long-term prognosis is directly related to LV size and systolic function[1-3]. In recent years, it has been increasingly apparent that LV diastolic dysfunction contributes to signs and symptoms of clinical heart failure with or without systolic dysfunction. LV dysfunction has also been reported in the subacute and late phase after myocardial infarction and it is becoming increasingly clear that abnormalities of diastolic function during AMI have a major role in affecting the prognosis of these patients. The term "diastology" is currently used to refer to the science and art of characterizing LV relaxation and filling dynamics and their integration into clinical practice[4]. However, until recent years the study of patients with diastolic dysfunction has suffered from the substantial difficulties inherent in diagnosing, measuring, quantitating and in following it over time. Moreover, the complexity of events encompassed by diastole[5], which are often difficult to control in the clinical arena, and the lack of data available to guide therapy, have hampered the widespread application of diastology in the clinical setting of AMI.

The advent of Doppler echocardiography and its complementary techniques have provided a bedside tool which yields reliable and useful measures of diastolic performance during AMI, placing such an assessment well within the grasp of every clinical echocardiographic laboratory. This review will focus on the role of Doppler echocardiography in the assessment of diastolic function and on the utility of Doppler-derived indices not only for diagnostic purposes but also for determining the clinical and prognostic impact of diastolic abnormalities observed during the evolving phases of AMI.

Physiologic and pathophysiologic background

The diastolic properties of a ventricle are defined by its curvilinear pressure-volume relation. Several variables affect this relation, with different factors being important at different times. Myocardial elasticity and geometry (size and thickness) are important throughout diastole, the other effects are superimposed on the pressure due to myocardial elasticity: during early diastole, active relaxation and the recoil effect of elastic energy stored in the myocardium from the previous systole (diastolic suction) are important; late in diastole ventricular interaction and the pericardium become important; viscoelastic properties of the myocardium play a small role during rapid filling and atrial contraction, and coronary vascular engorgement has a small effect late in diastole[6]. The mechanisms by which the compliance of a ventricle may change relate not only to the displacement of this relation (shift to a new pressure-volume curve) but also to the curvilinear nature of the diastolic pressure-volume relation. Thus, changes in the level of operating LV diastolic pressure may alter the compliance without changing the overall diastolic pressure-volume curve (Fig. 1)[7]. LV scar, hypertrophy and acute or chronic volume overload may each result in alterations in ventricular compliance through different mechanisms. Therefore, one of the important aspects of myocardial infarction is that it is accompanied by profound changes in diastolic properties of the left ventricle.

In the sequence of ischemic events, described by hemodynamic and clinical findings observed during acute occlusion of a major coronary artery, the earliest sign of myocardial ischemia is reflected by the occurrence of diastolic dysfunction, and only the ongoing ischemia with regional wall motion abnormalities results in systolic dysfunction[8]. Although the predominant diastolic abnormality induced by transient ischemia is impairment in relaxation[9], the diastolic filling pattern may change during AMI, resulting in a restrictive filling pattern[10,11]. Early invasive studies, performed almost three decades ago, showed an upward shift in the pressure-volume curve during AMI or ischemia as a result of an increase in resistance to filling or increased chamber stiffness[12]. Subsequent experimental studies have confirmed these findings also showing that diastolic dysfunction in large AMI may have a biphasic behavior with chamber stiffness increasing within 24 hours and reverting to normal after several days[13]. These changes in LV diastolic function may reflect primary alterations in the mechanical properties of the infarcted and noninfarcted regions or simply the ventricular filling on a steeper portion of its pressure-volume curve[13,14]. Thus, it is not surprising, in view of the aforementioned effects of ischemia on LV compliance, that early after myocardial infarction the filling pattern resembles the hemodynamic behavior of those conditions, such as constrictive pericarditis and restrictive cardiomyopathies, with "restrictive physiology". In the healing stages progressive rightward displacement of the pressure-volume relation occurs, indicating an increase in LV compliance.

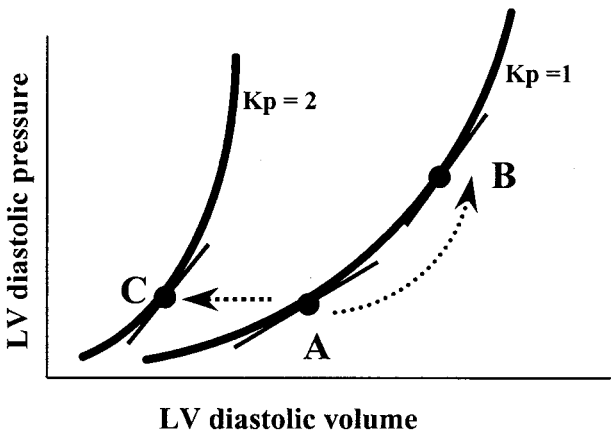

Figure 1. *The diastolic properties of a ventricle are defined by its curvilinear pressure-volume relation. The slope of a tangent to this curvilinear relation defines operative chamber stiffness at each level of filling pressure. Since diastolic pressure-volume relation can be fit by an exponential equation, a modulus of chamber stiffness (Kp) may be derived from the slope of the linear relation between chamber stiffness and pressure. Thus, chamber stiffness may change merely by virtue of a change in filling pressure (A → B) in the absence of any change in the modulus of chamber stiffness, or through a leftward shift to a different pressure-volume curve (A → C) as a result of an increase in the modulus of chamber stiffness. LV = left ventricular.*

Doppler echocardiographic assessment of diastolic function in acute myocardial infarction

Doppler echocardiography has emerged as a noninvasive modality that can be used to assess global LV filling dynamics providing a rapid, feasible, and simple bedside method of assessing and monitoring diastolic abnormalities in various cardiac diseases[15,16].

Animal experiments, human studies, and model studies[17] applying the laws of physics, have led to the general acceptance of the following equation of motion governing flow across the mitral valve:

$$\Delta P = (L)\, dQ/dt + R\,(Q)^2$$

where ΔP is the atrioventricular pressure difference, Q is the volume flow rate (ml/s), and L and R are inertial and resistive coefficients, respectively. L varies inversely with the area of the flow stream and R varies inversely with the square of the flow area.

It is clear from this equation that the transmitral flow pattern is uniquely related to the time varying atrioventricular pressure gradient and the impedance across the mitral valve. Thus, any physiological property that influences the diastolic-pressure behavior, does so via its influence on the transmitral pressure-flow relation. Other factors that exert their effects by modifying the atrioventricular pressure gradient are: heart rate, afterload, preload, age, exercise, calcium handling, and left atrial properties. The transmitral pressure-flow re-

lation offers the opportunity to understand the physical factors that determine the diastolic parameters measured by pulsed Doppler echocardiography (Fig. 2).

The Doppler recording of transmitral flow is characterized by a bipeaked filling pattern with individual velocity peaks, one occurring during rapid, passive ventricular filling in early diastole (E wave), and the other after atrial contraction in late diastole (A wave)[16]. The relative contribution of early and late filling is commonly expressed as the E/A ratio (early to late filling velocity). The transmitral velocity pattern remains the starting point of echocardiographic assessment of LV diastolic function, since it is easy to acquire and can rapidly categorize patients with normal or abnormal diastolic function by using E/A ratio which, normally, is > 1[18].

Two distinct patterns of abnormal LV filling are recognized in patients with heart disease[18]. The first and most common, is characterized by a decreased E wave peak velocity and deceleration rate with a concomitant increase in A wave peak velocity (E/A ratio < 1). The reduced early filling is caused by slower than normal LV relaxation, which decreases the early diastolic transmitral pressure gradient. This pattern occurs with normal or nearly normal left atrial pressure. Ventricular ischemia, hypertrophy and an aging ventricle are associated with a delay in LV relaxation[19]. The second LV filling pattern is characterized by an increase in E peak velocity and deceleration rate with a concomitant reduction in A velocity (E/A ratio >> 1). This second pattern is the result of a severe decrease in LV compliance and increased left atrial pressures. These two individual LV filling patterns were referred to as "impaired relaxation" and "restrictive filling" (Fig. 3), respectively, and have been shown to have a diagnostic and prognostic value in several disease states[20]. However, the hemodynamic components of each of the two aforementioned LV filling patterns may be associated causing a third hybrid pattern without echocardiographic evidence of dysfunction (E/A > 1), termed "pseudonormal"[18] (Fig. 3). The pseudonormal pattern is due to a restoration of the normal early diastolic LV pressure gradient due to an increase in left atrial pressure which compensates for the slowed rate of LV relaxation. Because of Doppler flow profile ambiguity caused by pseudonormalization, new Doppler applications have been proposed to provide additional insights into the assessment of diastolic function, such as pulmonary venous flow velocity, tissue and color M-mode Doppler recordings[21-26].

Normally, the pattern of pulmonary veins consists of two forward systolic (VP_S wave) and diastolic (VP_D wave) flow velocities of approximately equal magnitudes, with a short, low-velocity flow (VP_A wave) reversal into the veins after atrial contraction. In the presence of pseudonormalization the atrium is contracting against an increased afterload, thus favoring reversed flow (VP_A wave) into the pulmonary veins rather than forward transmitral flow (A wave)[21,22]. A pulmonary venous VP_A wave reversal greater in duration than the forward transmitral A wave has been shown to indicate an elevated LV end-diastolic pressure[21] and, thus, may reveal pseudonormalization of the transmitral E/A flow profile. In the early phase of anterior AMI, the simultaneous evaluation of transmitral filling pattern and pulmonary venous pattern has shown that a short deceleration time (DT ≤ 130 ms) of the early filling wave is indicative of elevated LV end-diastolic pressure despite an apparently normal E/A ratio[27]. This finding is in agreement with experimental data which have suggested that DT, measured by pressure-volume relation or by Doppler echocardiography, accurately assesses LV chamber stiffness[28,29]. Thus, not surprisingly, in clinical studies DT resulted more sensitive and specific than E/A ratio in assessing LV filling pressure in patients with LV systolic dysfunction after infarction[30].

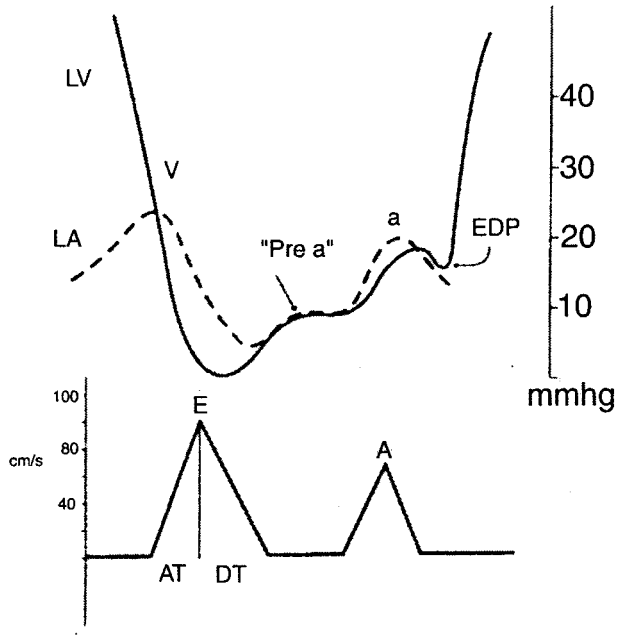

Figure 2. *Mitral flow starts when left atrial (LA) pressure falls below the left ventricular (LV) pressure and, as the pressure gradient develops, flow rapidly accelerates to reach its peak value, the E point. Shortly after the E point, the atrioventricular pressure gradient becomes zero and flow starts to decelerate under the action of a negative gradient. Finally, flow is again accelerated and decelerated by the atrial contraction and relaxation, the A wave. Indices of the transmitral flow pattern that have been found to be useful in the study of diastolic function include: E wave deceleration time (DT) and E/A ratio. AT = acceleration time; EDP = end-diastolic pressure.*

Figure 3. *Pattern of pulsed Doppler left ventricular inflow.*

Tissue Doppler echocardiography records systolic and diastolic velocities within the myocardium[31] and at the corners of the mitral annulus[23,24]. The velocity of annular motion reflects shortening and lengthening of the myocardial fibers along a longitudinal plane. A typical spectral display shows a velocity signal directed toward the LV centroid during systole (Sm) and two distinct signals directed away from the centroid during early (Em) and late (Am) diastole. The annular velocities are less influenced by transmitral pressure gradients than the flow velocities[32]. Accordingly, peak Em velocities are reduced in the presence of impaired relaxation, whether this abnormality occurs alone or in conjunction with pseudonormalization. Transmitral E wave velocity corrected for the influence of relaxation (i.e. the E/Em ratio) well relates to mean pulmonary capillary wedge pressure and may be used to estimate LV filling pressure[24] and, thus, to detect pseudonormalization. We have recently assessed diastolic function in the early phase of anterior AMI and found that patients with a short DT and pseudonormal pattern, as evaluated by a simultaneous measure of transmitral flow profile and pulmonary venous pattern, had an elevated E/Em ratio (14 ± 3), confirming an increase in LV end-diastolic pressure[27].

Finally, in the setting of diastolic dysfunction the rate of propagation of blood into the left ventricle is diminished, a phenomenon most readily evaluated by color M-mode Doppler[23]. Such color M-mode Doppler recordings reveal both early diastolic and atrial flow streams, the slopes of which are functions of the transit rate of intracardiac LV filling. In contrast to standard Doppler filling indices (E wave), the flow propagation velocity of early transmitral flow (Vp) measured by color M-mode Doppler has been shown to be relatively independent of preload. Thus, its value is equally lower both in patients with delayed relaxation and pseudonormalization[33]. Furthermore Vp is inversely correlated with the time constant of isovolumetric relaxation[23]. Therefore, the ratio of peak E velocity and Vp (E/Vp), after correction for the effect of LV relaxation, provides a good estimate of LV end-diastolic pressure[34,35].

Prevalence and time course of diastolic dysfunction in acute myocardial infarction

As shown recently, diastolic dysfunction was found in approximately 60% of all patients with AMI, and was associated with an "impaired relaxation" filling pattern in 40% and restrictive filling pattern in 25%[36]. The prevalence of a restrictive filling pattern, as assessed by Doppler transmitral flow profile and/or by a short DT, ranges from 13 to 26% in nonselected patients with AMI treated with medical therapy[36-39] and up to 35% in selected patients with anterior AMI[27]. These figures reflect different clinical characteristics of patients enrolled, since the size of the infarct zone has been shown to influence the diastolic filling, with the large infarcts exhibiting a restrictive filling pattern[11,13,40].

Serial Doppler assessment of DT in patients with AMI and restrictive filling pattern demonstrated that it transiently decreases on day 2 and subsequently increases[11,27,36]. In patients with anterior AMI successfully treated with direct coronary angioplasty and subgrouped, according to DT values assessed on day 3, in the restrictive ($\leq$ 130 ms) and nonrestrictive ($>$ 130 ms) LV filling pattern, we found an increase in DT values in both groups on day 7, and at 1 and 6 months[27]. However, the increase in DT was significantly higher in the restrictive group so that the differences between the two groups were less pronounced at 1 and 6 months and statistically not significant. Overall, these findings are in agreement with experimental evidence suggesting an early increase in chamber stiffness that subsequently returns to normal[13]. These evolutionary changes in filling pattern may be explained by the healing and the remodeling process (see below), rather than by a gradual recovery in diastolic function after reperfusion. As healing progresses, the left ventricle becomes more compliant and dilates, inducing relevant changes in mitral flow velocities, such as prolongation of DT. Thus, serial changes in filling pattern after AMI parallel the evolutionary changes in LV dimensions.

In addition to the infarct size, several other variables, including stunned myocardium, recurrent ischemia and medical therapy, may affect the time course of LV diastolic function. Wijns et al.[41] studied patients undergoing coronary angioplasty and demonstrated that regional diastolic function remained significantly impaired for at least 12 min after balloon inflation and deflation. This finding is in agreement with experimental data demonstrating that the LV diastolic properties may remain reversibly impaired for prolonged periods of time (24 hours) after transitory coronary occlusion suggesting a "diastolic stunning", which is an equivalent of the well-known systolic phenomenon[42]. Finally, in patients with anterior AMI Garadah et al.[43] demonstrated a reversal of the restrictive pattern of diastolic filling in response to a short infusion of nitroglycerin. Depending on the interaction of these factors, the timing of maximal prevalence of restrictive pattern during the acute phase of myocardial infarction may vary. This may in part account for the different results achieved in different studies: in some studies[11] a restrictive pattern was found most frequently on day 2, whereas in others[38] on day 7 after the index infarction.

Diastolic dysfunction in acute myocardial infarction and left ventricular remodeling

The most common stimulus for myocardial hypertrophy and remodeling is hemodynamic overload. Abnormal mechanical stresses on cardiac myocytes may be

a direct stimulus for myocardial remodeling[44]. After relatively large infarcts there is a significant impairment in LV hemodynamics. However, only the increase in LV end-diastolic pressure has been found to be positively correlated with infarct size chronically[45]. The changes in this parameter in combination with the increase in chamber diameter result in a marked elevation of diastolic wall stress that parallels infarct dimension[45].

The two structural mechanisms which have been identified in the genesis of ventricular remodeling following myocardial infarction are the side-to-side slippage of cells within the nonviable and viable ventricular tissue[46], and the pattern of the cellular hypertrophic response in the surviving myocardium[45]. Although, both these processes have been viewed as an adaptation to increased cardiac load, the mechanism by which initial chamber dilation alters the global loading conditions has still to be clarified. Numerous studies have demonstrated in the early stages of coronary occlusion that there are marked alterations in diastolic behavior, with impaired ventricular relaxation and greatly elevated myocardial stiffness[47]. These changes in ventricular chamber properties arise from a profound regional dysfunction and the resultant asynchrony between ischemic and normal myocardium. These abnormalities are followed by elevation of ventricular end-diastolic pressure. Increased myocardial stretch may also promote an unfavorable neurohormonal pattern which is a major determinant of the remodeling process and of disease progression[48,49]. Interestingly, the time course of the restrictive LV filling during the acute phase of myocardial infarction closely mirrors the biphasic pattern of brain natriuretic peptide release observed in patients with large AMI[50].

Therefore, in view of the aforementioned physiological correlation between DT and LV function/filling, we have recently correlated serial changes in filling pattern with serial changes in LV dimension after reperfused anterior AMI to assess whether a restrictive filling pattern, as expressed by a short DT (≤ 130 ms) assessed on day 3 after the index infarction, may predict postinfarction LV remodeling[27]. We found that serial changes in the filling pattern after AMI paralleled the evolutionary changes in LV dimensions. In the group of patients with a short baseline DT the filling pattern changed from restrictive to "normal" at 6 months after the index infarction. These evolutionary changes may be explained by the healing and remodeling processes. In the early phases of AMI the diastolic filling pattern may be restrictive due to an increase in LV stiffness, left atrial and LV diastolic pressure. As healing progresses, the left ventricle becomes more compliant and dilates, inducing relevant changes in mitral flow velocities, such as prolongation of DT[51]. In our series, all but 2 patients with LV dilation at 6 month follow-up had shortened DT (≤ 130 ms) at day 3 after the index infarction, while only 1 patient with a DT ≤ 130 ms did not develop LV dilation[27]. Finally, a short DT was the most powerful predictor of LV remodeling even after controlling for infarct size, and the degree of LV dilation was related to the severity of impairment of LV filling[27]. These findings are in agreement with a very recent experimental study[52]. In a canine model of infarction and reperfusion, Gerber et al.[52] correlated infarct size and extent of microvascular obstruction with alterations in myocardial strains by magnetic resonance tagging. They found that in the early healing phase of AMI increased amounts of microvascular obstruction correlated significantly with altered myocardial strains both in infarcted and in adjacent noninfarcted regions up to 48 hours after reperfusion. A possible explanation for the observed alterations in myocardial strains could be enhanced stiffness of infarcted tissue with microvascular obstruction. Thus, these results suggest that myocardial stiffening in regions with microvascular obstruction may have an adverse effect on LV geometry and segmental function, ultimately resulting in increased LV remodeling[52]. These results confirm and expand our clinical observation[27] that an increased LV stiffness, as measured by Doppler echocardiography, adversely affects the remodeling process, providing the critical linkage between the restrictive filling pattern and clinical events after AMI as seen in some observational studies[36-38].

Finally, it is possible that the LV filling pattern will also prove useful in detecting the late structural remodeling. In fact, the excessive fibrous tissue formation at sites remote to the myocardial infarction, that usually accompanies LV remodeling, reduces tissue distensibility which in turn affects LV diastolic function[53]. Our preliminary data in patients with postinfarction LV remodeling support this hypothesis. In patients with postinfarction LV dilation (n = 12) we observed, at 30 month follow-up, a significantly higher serum concentration of amino terminal propeptide of type III procollagen (PIIINP), which has been used to address collagen turnover in various cardiac diseases including AMI[54], compared to patients (n = 28) without postinfarction LV dilation (4.76 ± 1.36 vs 3.66 ± 0.76 ng/ml, p = 0.003) (personal data). Interestingly, the LV filling pattern became more restrictive in patients with postinfarction LV dilation and high PIIINP (DT from 192 ± 53 to 153 ± 49 ms, p = 0.05) from 6 to 30 months. These late changes in LV filling pattern occurred in the absence of recurrent ischemia and further significant alterations in LV geometry. Future large scale serial Doppler echocardiographic studies are needed to assess if monitoring of LV diastolic function will prove useful in detecting late structural changes during the LV remodeling process.

Diastolic function in acute myocardial infarction and prognosis

In recent years, a few preliminary studies have shown that the restrictive filling pattern, assessed by Doppler

echocardiography, is an independent predictor of adverse outcome in patients with AMI. Nijland et al.[38] reported short DT to be the best single predictor of cardiac death in hospital survivors after AMI: the survival rate at 1 year was 100% in the "nonrestrictive" patients and only 50% in the "restrictive" group; moreover, after 1 year there was a continuing divergence of mortality, resulting in a 3 year survival of 100 and 22% respectively[38]. Poulsen et al.[36] reported a 1 year cardiac death rate of 43% among patients with pseudonormal/restrictive LV filling pattern early after AMI, while none of the patients without pseudonormal/restrictive died[36]. Moreover, heart failure during hospitalization and hospital readmission for heart failure during 12 months of follow-up occurred in 71 and 21%, respectively, of patients with pseudonormal/restrictive LV filling, compared with 50 and 5%, respectively, of patients with initial impaired relaxation LV filling. No patient with initial normal LV filling had heart failure during hospitalization or follow-up[36]. More recently, Moller et al.[55] have shown that the presence in the early phase of myocardial infarction of elevated LV end-diastolic pressure, as assessed by an E/Vp ratio ≥ 1.5 at color M-mode Doppler, is associated with a worse prognosis (survival rate 58 vs 98% in patients with an E/Vp ratio < 1.5). However, a short DT (< 140 ms) early after AMI remained the most powerful predictor of in-hospital cardiac death[55]. In these studies patients were treated with thrombolysis or conservative medical therapy and no information was provided about the perfusional status of the infarct-related artery.

In agreement with the aforementioned studies, in our experience a short DT detected in the early phase of anterior AMI treated with primary angioplasty, still retains its prognostic significance even after optimal recanalization of the infarct-related artery and late persistent patency. We followed up 104 patients, 34 with short DT (≤ 130 ms) and 70 with DT > 130 ms, for 32 ± 10 months. The cumulative mortality rate was 21% in the restrictive group and 2.8% in the nonrestrictive group ($p = 0.003$). Overall, cumulative events (defined as death, reinfarction or congestive heart failure) were significantly higher in patients with short DT than in patients without short DT (56 vs 7%). However, compared to previous studies[36,38,55], performed mainly on thrombolyzed patients, the outcome rate was lower. Thus, a relative long-term protective effect of mechanical reperfusion and persistent late patency on clinical outcome could be hypothesized in some patients[56]. Since LV volumes, in restrictive patients, increased at 6 months but remained unchanged from 6 to 24 months, as well as diastolic and systolic eccentricity indexes, it is reasonable to speculate that mechanical reperfusion and persistent late patency may have blunted the remodeling process, or at least attenuated its effects on LV shape and geometry, exerting a positive influence on the prognosis[56].

Conclusions

LV diastolic dysfunction is present in the evolving phases of myocardial infarction. The problem of detection and quantification of diastolic dysfunction in AMI patients has been substantially resolved since newer applications in echocardiography are revolutionizing the study of diastolic function in this setting.

Determination of the pattern of LV filling by Doppler echocardiography provides important information about LV diastolic function in AMI patients. Clinical data gathered so far demonstrate that Doppler-derived LV filling, specifically the restrictive filling pattern, is a powerful independent predictor of late LV dilation and, most importantly, of cardiac death in patients with AMI and clearly indicate the need for evaluating and monitoring LV diastolic function in these patients[57].

It is now possible to predict prognosis, estimate filling pressure and guide therapy by Doppler echocardiography and its complementary techniques. Preliminary studies performed in patients with dilated cardiomyopathy or congestive heart failure showed that reversibility of restrictive filling is associated with better outcome[58]. Thus large scale studies, utilizing simple and easy to measure Doppler indexes of LV filling are needed to assess the efficacy of medical therapy in patients with acute LV diastolic dysfunction during AMI.

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