Doppler evaluation of left ventricular filling in congestive heart failure

T. Masuyama and R. L. Popp*

First Department of Medicine, Osaka University School of Medicine, Suita, Japan; *Cardiology Division, Department of Medicine, Stanford University School of Medicine, Stanford, California, U.S.A.

Introduction

Assessment of left ventricular diastolic function has become a subject of great interest. However, while the importance of left ventricular diastolic dysfunction is increasingly appreciated, methods for measuring left ventricular filling and the flow-pressure-volume relationship in patients are limited. Echocardiography has been used increasingly as a method for investigating left ventricular function, and the results of various approaches employing this technique are summarized in this review.

Why do we measure left ventricular diastolic function in patients with congestive heart failure?

The heart contracts in systole and relaxes and expands in diastole. Because the heart supplies blood to peripheral organs, left ventricular ejection performance is obviously important, and this function has been emphasized when assessing the diseased heart[1,2]. However, assessment of diastolic function is probably as important as assessment of systolic function regarding both early detection of left ventricular abnormalities and understanding the pathogenesis of congestive heart failure[3-6]. Left ventricular relaxation abnormalities usually precede both systolic dysfunction and decreased passive compliance in most common conditions[3,7,8]. Therefore, it may be the only detectable abnormality in the early stage of many left ventricular myocardial diseases[3,7-10]. Progressive or advanced left ventricular diastolic dysfunction can cause congestive heart failure even without systolic dysfunction[4-6]. Moreover, diastolic dysfunction still plays an important role in the genesis of the symptoms of congestive heart failure and in the prediction of disease prognosis in patients with left ventricular systolic dysfunction[4,6,11-14].

Almost 15 years have passed since the Doppler mitral inflow velocity pattern was first observed to reflect left ventricular diastolic behaviour[9]. The pattern signals change in loading conditions in addition to intrinsic left ventricular diastolic function, indicating that left ventricular filling is related to, but not identical to, ventricular diastolic function. The pattern has been scrutinized quantitatively in many studies so that these interactions can be better understood[15-18]. Doppler flow velocity patterns assess left ventricular filling extremely sensitively, but more should be made of the potential pitfalls of using Doppler indexes in drawing direct conclusions about underlying diastolic function. Pattern recognition, rather than quantitative analysis, has gained wide popularity[19]. Flow velocity records are classified as representing a relaxation abnormality pattern, a normal or pseudonormalized pattern or a restrictive pattern (Fig. 1)[19]. It has been quite difficult to distinguish between a truly normal pattern and a similar one resulting from a complex interaction of myocardial and haemodynamic factors in an individual patient. Recent work has shed light on this distinction, especially in patients with congestive heart failure.

How do we assess the mitral flow velocity pattern?

The mitral flow velocity pattern may be recorded either at the tips of the mitral leaflets or at the mitral anulus; sometimes using colour Doppler or two-dimensional echo guidance from the apical approach. Location of the sample volume is important because the flow velocity is usually higher at the mitral leaflet tips than at the mitral anulus[20]. Flow velocity at the mobile mitral leaflet tips appears to reflect the instantaneous transmitial pressure gradient, while flow velocity at the larger and more...
ECG

Mitral flow

AC MO

IVRT

Relaxation abnormality pattern

Normal or pseudonormal pattern

Restrictive pattern

Figure 1 Diagram illustrating mitral flow velocity patterns. The relaxation abnormality pattern (left panel) is characterized by a prolonged isovolumic relaxation time (IVRT) from aortic valve closure (AC) to mitral opening (MO), decreased peak early diastolic flow velocity (E) and its ratio to peak flow velocity at atrial contraction (A), prolonged deceleration time of the early diastolic filling wave and increased A. Characteristics of the restrictive pattern (right panel) includes shortening of IVRT, increases in the E and E/A ratio, shortening of deceleration time and a decrease in A. The pseudonormalized pattern may exhibit a pattern that resembles normal. These patterns represent a dynamic continuum and may change from one pattern to another as loading conditions and disease status alter.

fixed mitral anulus reflects left ventricular volume change. Analysis of the flow velocity pattern at the mitral leaflet tips has been studied most in terms of detection of early left ventricular relaxation abnormalities and in recognizing abnormal loading conditions in the more advanced stage of disease. Left ventricular relaxation was originally considered the major determinant of the mitral flow velocity pattern, particularly in the early stage of left ventricular disease, when systolic function had not deteriorated and the change in diastolic function was too subtle to produce secondary adaptive alterations in haemodynamics. In the presence of a mild myocardial relaxation abnormality, cardiac output and total ventricular filling volume is maintained by filling redistribution from early to late diastole without any compensatory increase in mean left atrial pressure. This may be explained as follows. Mild myocardial relaxation abnormality is associated with a slowed left ventricular pressure fall, even after mitral valve opening, and left atrial pressure remains unlevated because the total filling volume in the preceding cardiac cycle was maintained by increased filling in the atrial contraction phase. Thus, the transmitral pressure gradient just after the mitral valve opening is decreased, compared to the normal state. This accounts for the decrease in the early diastolic mitral flow velocity (E-velocity) (Fig. 2). With a mild myocardial relaxation abnormality, left ventricular relaxation rate slows but relaxation extent is unaltered, so the myocardial tension continues to decrease for a longer period than in normal hearts, and the process may extend to mid-to-late diastole. Decreased left ventricular filling means decreased left atrial emptying, which prevents a rapid fall in left atrial pressure. Additionally, decreased left ventricular filling results in a lower or more limited left ventricular pressure rise in the pressure-volume relationship than in normal hearts, even though the ventricle is slightly stiffened because of the mild myocardial relaxation abnormality. These factors, that is, prolonged or persistent decrease in myocardial tension, gradual left atrial pressure drop and slowed left ventricular pressure rise due to reduced left atrial emptying and left ventricular filling in early diastole, work to lengthen the deceleration time of the early diastolic mitral flow wave.

Left atrial volume just before the atrial contraction is enlarged because of decreased atrial emptying in early diastole. Left ventricular pressure remains stable because of decreased ventricular filling in early diastole. Thus, mitral flow velocity at atrial contraction is enhanced, presumably through the Frank-Starling mechanism of the left atrium. Because total left ventricular filling is maintained, left atrial pressures may well be normal following atrial contraction, during ventricular systole and at subsequent mitral opening. Thus, we may consider a pattern characterized by decreased E-velocity, prolonged deceleration time and increased A-velocity as indicative of a mild myocardial relaxation abnormality. Such a pattern is not specific to any particular heart disease, but may be observed in any patient with a mild left ventricular relaxation abnormality, such as occurs typically in the elderly, in those with hypertension, hypertrophy, cardiomyopathy, or ischaemic heart disease.

If myocardial relaxation is significantly impaired, total ventricular filling cannot be maintained simply by the mechanism described. In this case, left atrial pressure is shifted upward, which tends to normalize the trans-mitral pressure gradient in early diastole. Therefore, elevation of left ventricular pressure and increased rate of left ventricular pressure fall occur just after mitral valve opening, as a result of left atrial pressure elevation.
at mitral valve opening. This accounts for the normalization of mitral E-velocity. Left ventricular filling and left atrial emptying following mitral valve opening are more regular, and therefore left ventricular pressure increase and left atrial pressure fall are also more regular or steeper than normal, because of the stiffened left ventricle and atrium. Thus, deceleration time is normalized or shorter than normal. Left atrial pressure just before atrial contraction is normal or slightly increased with mild left atrial enlargement. Left ventricular pressure just before the atrial contraction is higher than normal because of the normal ventricular filling into the stiffened ventricle in early diastole. Thus, enhanced left atrial contraction through the Frank-Starling mechanism and increased impedance from the ventricle are probable explanations for the normalized A-velocity in the presence of moderate myocardial relaxation abnormalities.

Early diastolic filling is maintained because of a compensatory increase in left atrial pressure even when myocardial relaxation is severely impaired. However, when there is a similar amount of ventricular filling in the stiffened ventricle, this causes an even steeper ventricular pressure increase, as compared with the ventricles with moderately impaired myocardial relaxation. Thus, when myocardial relaxation is severely impaired, equalization of the left ventricular–left atrial pressure gradient occurs earlier, yielding a shorter deceleration time, than in moderately impaired myocardial relaxation. In these circumstances, a stiff ventricle, filled at elevated pressures, results in highly elevated left ventricular pressure just before atrial contraction. Thus, the sharp increase in impedance from the ventricle results in reduced filling at atrial contraction, and the deceleration time is prolonged, which is consistent with the Frank-Starling mechanism. As noted above, the mitral inflow velocity pattern associated with severely impaired left ventricular myocardial relaxation is characterized by a normal E-velocity, abnormally shortened deceleration time and markedly decreased or absent A-velocity.

The mitral flow velocity pattern changes with the degree of myocardial relaxation abnormality, and the presence of either a mild or a severe myocardial relaxation abnormality is identified by analysis of mitral inflow velocity patterns. In contrast, moderate myocardial relaxation abnormality may not be obvious from the mitral inflow velocity pattern because the pattern appears normal (pseudonormalized) in spite of a significantly diseased ventricle. In addition, the pattern can be affected dramatically by changes in drug therapy (diuretics and vasodilators) without inferring any change in the underlying left ventricular diastolic function, particularly because of the strength of preload dependency of the pattern.

Differentiating the truly normal pattern from a pattern that only appears to be normal

Before referring to pseudonormalization as described in individual studies, the normal values of mitral flow velocity parameters have to be determined. Mitral flow velocity parameters are affected by ageing. Ageing is associated with decreases in E-velocity and the E/A ratio, an increase in A-velocity and a prolonged deceleration time. The effect of ageing is strong enough for normal values to be examined as a function of age. However, we took the E/A ratio of $<0.5$ and a deceleration time of $>200$ ms as a relaxation abnormality pattern, and the E/A ratio of $>2.0$ and deceleration time of $<100$ ms as a restrictive pattern, in subjects about 50 years old. The intermediate values and patterns should be either normal or pseudonormal, but it is often difficult to differentiate truly normal filling patterns from
pseudonormal filling patterns in the clinical setting. A priori knowledge of the presence or absence of left ventricular disease may help the differentiation because a normal filling pattern in patients with a presumed advanced left ventricular relaxation abnormality is suggestive of the presence of elevated left ventricular filling pressure and pseudonormalization. However, it is not necessarily easy to recognize a left ventricular relaxation abnormality solely from the clinical characteristics. Thus, it is important to differentiate truly normal filling patterns from pseudonormal filling patterns in individual patients. Currently, at least five techniques have been proposed to differentiate the normal filling pattern from a pattern that appears normal despite abnormal ventricles.

(i) Pulmonary venous flow velocity pattern

Current ultrasound machines achieve a reasonably high signal-to-noise ratio of pulsed Doppler signals, which enables adequate recording of the right upper pulmonary venous flow velocity pattern, even by the transthoracic approach\[28,30-34\] (Fig. 3). The pulmonary venous flow velocity pattern may be helpful because the peak diastolic antegrade flow velocity of $\geq 60$ cm $\cdot$ s$^{-1}$, or the ratio of peak systolic to diastolic antegrade flow velocity of $< 0.75$, is indicative of pseudonormalization of the mitral flow velocity pattern (Fig. 4). According to our experience, only 60% of pseudonormalization can be identified with these criteria\[10,35\]. Because there is no established way to identify pseudonormalization, this method is clinically useful in spite of the relatively low value of the detection ratio. Analysis of the pulmonary venous retrograde flow wave at atrial contraction may also be useful both because its peak velocity increases with left ventricular end-diastolic pressure\[30\] and because the mitral A-wave duration gets shorter relative to the pulmonary venous A-wave duration in patients with higher left ventricular end-diastolic pressure\[36\] (Fig. 5). However, frequently the pulmonary venous retrograde A-wave is unrecognizable because the flow signal overlaps with or is masked by the strong signals derived from the movement of surrounding structures.

(ii) Valsalva manoeuvre

It has been observed that the influence of loading conditions has been used to attempt to unmask this pseudonormalized pattern. Dumesnil et al. recorded the mitral flow velocity pattern at baseline and during phase II of the Valsalva manoeuvre, when flow velocity reduction was maximal, in patients with and without evidence of cardiac ischaemia, prior myocardial infarction or hypertension\[37\]. Their findings confirm their hypothesis that reduced venous return markedly reduces both Doppler E and A-waves proportionately in normals (E/A ratio unchanged). Those expected to have diastolic dysfunction should have a marked reduction in E-wave velocity during the Valsalva manoeuvre but A-wave velocity should decrease only slightly. Such changes were observed in 33 of 65 patients with an apparently normal pattern at rest, and suggested that the pseudonormalization was unmasked by the intervention. Since elevated left atrial pressure may ‘normalize’ the mitral flow velocity pattern, it is reasonable to expect that a reduction in venous return and left atrial pressure will unmask persistent myocardial abnormalities.

(iii) M-mode LV echocardiograms

Digitized M-mode echo indexes of early diastolic filling (peak wall thinning rate and peak rate of left ventricular dimension increase) and Doppler indexes of the mitral flow velocity pattern were not necessarily indicative of abnormalities in patients with left ventricular hypertrophy secondary to aortic stenosis\[38\]. M-mode echo indexes were more consistently abnormal than mitral flow velocity indexes, suggesting that M-mode echo indexes may be used to detect pseudonormalization of
Figure 4  Mitral and pulmonary venous flow velocity patterns in patients with a pseudonormalized mitral flow velocity pattern (a) and (b). Both patients had apparently normal mitral flow velocity patterns (top panels) despite breathlessness at rest or at mild exertion. Pulmonary venous flow velocity patterns showed an increase in peak diastolic antegrade flow velocity (D). Peak systolic antegrade flow velocity (S) increased in (a) but decreased in (b). The height of the S wave appears to be related to left ventricular systolic function. Left ventricular fractional shortening was normal in (a), but was severely decreased in (b). PCG = phonocardiogram.

the mitral flow velocity pattern (Fig. 6). Most recently, the advent of tissue Doppler imaging has made it easier to measure the peak rate of left ventricular dimension increase and/or wall motion velocity. The M-mode tissue Doppler index of early diastolic filling is obtained without tracing the endocardial edge, and may be useful in identifying pseudonormalization.\cite{30} The value of the tissue Doppler index has not yet been validated and therefore requires future confirmation.

Doppler measures a velocity rather than a filling rate, and M-mode measures a dimension rather than a volume. Thus it is likely that this may explain the apparently disparate results. However, the tissue Doppler method has inherent serious limitations regarding regional vs global function.

(iv) Estimates of LV dV/dt

If the left ventricular area or volume, rather than the M-mode dimension or wall thickness, is used to assess rates of change, some limitations of the above methods may be overcome. The recent introduction of automatic border detection techniques is promising in this regard. The abnormal relaxation (decreased rapid early filling rate) pattern was sometimes identified by acoustic quantification in patients with left ventricular hypertrophy who had an apparently normal mitral flow velocity pattern.\cite{40} These data strongly suggest that the mitral flow velocity pattern does not reflect left ventricular volume change, at least in certain circumstances, and that pseudonormalization of the mitral flow velocity pattern may be noted by detecting the discrepancy.

(v) Intraventricular flow dynamics

The early diastolic flow velocity measured at the mitral leaflet tips is maintained up to 2 to 3 cm towards the apex in healthy subjects, but it immediately decreases as blood moves towards the apex in patients with presumed
Mitral and pulmonary venous (PV) flow velocity patterns in a healthy subject (left panels) and in a patient with elevated left ventricular end-diastolic pressure (right panels), showing that the duration of the flow at atrial contraction in the mitral flow velocity pattern is shortened in patients with elevated left ventricular end-diastolic pressure and that the duration of the reverse flow at atrial contraction in the pulmonary venous flow velocity pattern is prolonged in patients with elevated left ventricular end-diastolic pressure. Rossvoll and Hatle showed that left ventricular end-diastolic pressure is likely to be higher than 15 mmHg if flow wave at atrial contraction is wider in the pulmonary venous than in the mitral flow velocity patterns.

Figure 5

M-mode left ventricular echocardiogram and mitral flow velocity pattern in a patient with hypertensive heart failure. In this patient the M-mode left ventricular echocardiogram shows a marked decrease in the early diastolic ventricular expanding and wall thinning rate, while the mitral flow velocity pattern shows an increase in E-velocity and a decrease in A-velocity (restrictive pattern).

Figure 6

left ventricular diastolic dysfunction\(^{(43)}\). Analysis of M-mode colour Doppler imaging provides a straightforward explanation of intraventricular flow dynamics, because the information regarding instantaneous flow velocities along the ultrasound beam is displayed using a colour scale in a distance–time domain (Fig. 7). M-mode colour Doppler imaging also provides information about the timing regarding transmission of flow within the ventricular cavity\(^{(42,43)}\). In patients with a relaxation abnormality, the slope of the flow wave front during early diastolic filling was gradual, suggesting slow transmission of the flow during early diastolic filling\(^{(42)}\). In addition, the time difference between occurrence of the peak early diastolic filling velocity at the mitral leaflet tips and at the apex is longer in the failing left ventricular than in the normal left ventricular reflecting impaired relaxation\(^{(43)}\). The M-mode colour Doppler indexes of left ventricular filling are not affected by left ventricular
size but they are affected by left ventricular systolic function. Analysis of M-mode colour Doppler imaging of intraventricular flow dynamics may be useful in detecting a pseudonormalized mitral flow velocity pattern because transmission of the flow during early diastolic filling is slow even in patients with a pseudonormalized mitral flow velocity pattern.

Clinical significance of pseudonormalization

The restrictive pattern has been shown to be a significant predictor of poor prognosis in patients with amyloidosis, dilated cardiomyopathy and congestive heart failure. Prognosis of patients with the pseudonormalized pattern also may be poor because the pseudonormalized pattern has been observed in advanced stages of certain heart diseases. Currently, no data are available regarding the prognosis of those with and without a pseudonormalized mitral flow velocity pattern, mainly because of the difficulty of definition and detection of pseudonormalization. Therefore, improved knowledge and understanding of the factors causing pseudonormalization of the mitral flow velocity pattern should provide further insight into the evaluation and management of such patients.

Conclusions

Evolutionary changes in the mitral flow velocity pattern, in association with progression of left ventricular relaxation abnormalities, are complicated. This is because left ventricular relaxation abnormalities, particularly in advanced stages, cause haemodynamic adjustments and because the underlying abnormalities and compensatory haemodynamic adjustments each affect the mitral flow velocity pattern. From the clinical viewpoint, it is important to assess not only left ventricular relaxation per se but also the degree of haemodynamic adjustment. If a pseudonormalized or restrictive mitral flow velocity pattern is detected, we may conclude that the abnormalities are sufficiently significant to have induced haemodynamic adjustment, primarily through elevation of left atrial and/or left ventricular end-diastolic pressure. This review summarizes several potential methods of distinguishing pseudonormalization of the mitral flow velocity pattern. Although future studies in this field are still necessary for a better understanding of the complex factors involved, analysis of left ventricular diastolic filling is a promising method of providing novel information for the evaluation and management of patients with cardiac disease.

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References


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Innervation and effects of vasoactive substances in the coronary circulation

O. Saetrum Opgaard, S. Gulbenkian* and L. Edvinsson

Department of Internal Medicine, University Hospital of Lund, Lund, Sweden; *Department of Cell Biology, Gulbenkian Institute of Science, Oeiras, Portugal

Introduction

Ischaemic heart disease, one of the main causes of morbidity and mortality, was originally considered to result from atherosclerotic plaques. Later arterial spasm was also thought to be involved1. Since then, clinical as well as haemodynamic, angiographic, scintigraphic and metabolic studies have suggested that coronary arterial spasm may play a role in the aetiology of ischaemic heart disease2. It has also been demonstrated how certain segments of human coronary arteries, and particularly sites with evidence of arteriosclerosis, can be more sensitive than others to vasoconstrictive agents3. Furthermore, severe coronary spasm has been demonstrated to induce sudden progression of organic stenosis4. Of the mechanisms behind coronary artery spasm, it is known that coronary resistance can be modified through the action of perivascular, endothelial and humoral vasoactive substances5. With the development of histochemical techniques demonstrating catecholamines and acetylcholinesterase activity, there is evidence of noradrenergic, and presumably cholinergic nerves supplying the coronary vasculature6. In addition, the use of immunocytochemical techniques at both the light and electron microscopy levels have enabled the identification of several neuropeptides in specific populations of efferent and afferent nerves innervating coronary vessels7, whereas immunoreactivity to endothelin has been detected in the endothelial layer of human coronary arteries and veins8.

Until recently, little attention has been paid to the eventual role of the coronary venous bed in the regulation of coronary blood flow. Several studies have shown, however, that coronary venous pressure affects coronary arterial blood flow, capillary pressure and intramyocardial tissue pressure9, whereas immunoreactivity to endothelin has been detected in the endothelial layer of human coronary arteries and veins10.

The present review focuses on the nervous innervation of coronary arteries and veins, and discusses functional aspects of some of the more important vasoactive substances.