UPDATE IN RADIOLOGY

Analysis of left ventricular diastolic function using magnetic resonance imaging

G.C. Fernández-Pérez\textsuperscript{a,*}, R. Duarte\textsuperscript{b}, M. Corral de la Calle\textsuperscript{a}, J. Calatayud\textsuperscript{c}, J. Sánchez González\textsuperscript{d}

\textsuperscript{a} Servicio de Radiología, Complejo Asistencial de Ávila, Ávila, Spain
\textsuperscript{b} Servicio de Radiología, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal
\textsuperscript{c} Servicio de Radiología, Hospital POVisa, Vigo, Pontevedra, Spain
\textsuperscript{d} Clinical Science, Philips Healthcare, Madrid, Spain

Received 28 October 2010; accepted 4 September 2011

KEYWORDS
Magnetic resonance; Systolic function; Diastolic function; Transmital flow

Abstract
Heart failure is not always due to an alteration in systolic function, and a diastolic dysfunction could explain many cases of heart failure with a normal systolic function. Diastolic function depends on the left ventricular filling capacity to ensure a normal stroke volume. It is routinely measured with transthoracic echocardiography, as it is an easily accessible non-invasive test. The magnetic resonance imaging (MRI), using flow sequences, shows good agreement with the echocardiography, analysing the diastolic function in a practical way, by the flow into the mitral valve and pulmonary veins. In this sense, the analysis of diastolic function should be added as part of a routine cardiac MR examination.
© 2010 SERAM. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE
Resonancia magnética; Función sistólica; Función diastólica; Flujo transmitral

Análisis de la función diastólica del ventrículo izquierdo mediante resonancia magnética

Resumen
La insuficiencia cardíaca no siempre es debida a una alteración sistólica, y una disfunción diastólica puede explicar muchos casos de insuficiencia cardíaca con función sistólica normal. La función diastólica depende de la capacidad de llenado del ventrículo izquierdo para garantizar un volumen latido normal. Se mide rutinariamente con la ecocardiografía transtorácica, ya que se trata de una prueba no invasiva y de gran accesibilidad. La resonancia magnética (RM), utilizando secuencias de flujo, muestra una buena concordancia con la ecocardiografía, analizando la función diastólica de forma práctica, a través del flujo en la válvula mitral y las venas pulmonares. En este sentido, el análisis de la función diastólica debería añadirse como parte de un examen rutinario de RM cardíaca.
© 2010 SERAM. Publicado por Elsevier España, S.L. Todos los derechos reservados.

* Corresponding author.
E-mail address: gabriel.fdz.perez@gmail.com (G.C. Fernández-Pérez).

2173-5107/$ - see front matter © 2010 SERAM. Published by Elsevier España, S.L. All rights reserved.
Introduction

The heart function depends substantially on a pump mechanism where blood is received at low pressure during diastole and is ejected at high pressure during systole. A patient has congestive heart failure, which implies that the cardiac output is low and the ejection fraction (EF) is reduced. However, congestive heart failure is defined as a "pathophysiology syndrome, originated by a heart disorder that causes the inability to fill or pump blood to the appropriate levels, and if achieved, it is at the expense of a chronic elevation of the ventricular filling pressure". This definition not only takes into account anomalies of the pump mechanism or expulsion of blood, but also of the ventricular filling. The left ventricular filling capacity, consequent to the blood flow at low pressure, is a complex mechanism that depends on multiple factors, which can be summarized into three: ventricular relaxation following systole (isovolumic relaxation); ventricular compliance (mid diastole) and pericardial constriction. Any anomalies in these mechanisms will alter diastole resulting in diastolic dysfunction. Diagnosis of congestive heart failure secondary to diastolic dysfunction requires three criteria: (a) presence of signs and symptoms of heart failure; (b) normal or slightly reduced EF of the left atrium (EF ≥ 50%), and (c) increase in pressure of the diastolic filling. This diastolic dysfunction would explain how almost 40% of all patients with common signs of congestive heart failure have a practically normal EF.

The purpose of this study is to review the pathophysioloogy of diastolic dysfunction and the most common associated causes, illustrating with examples how to analyze it and measure it using MR.

Physiology aspects of the diastole

The ventricular diastole has 4 defined phases (Fig. 1):

- Isovolumic relaxation: time when the ventricle relaxes while the valves are closed. A rapid fall of intraventricular pressure occurs but volumes remain unchanged. It is similar to a suction effect.
- Rapid ventricular filling: intraventricular pressure falls causing the mitral valve to open and rapid blood flow and filling of the left ventricle (LV) occurs. Under normal conditions, it participates in 80–90% of the ventricular filling.
- Diastasis: subsequently to this rapid ventricular filling, pressure between the atrium and the ventricle becomes equal. The left atrium acts only as a passive channel, not having a direct influence in the filling; consequently, there is only blood passage through the pulmonary veins.
- Late ventricular filling (atrial contraction): this phase begins with an atrial contraction or atrial systole and ends with the closure of the mitral valve. It participates in approximately 10–20% of the ventricular filling. During this phase, the ventricular filling not only depends on the LV distension capacity but also on the resistance of the pericardium.

Ventricular relaxation is an active process that has an influence on the isovolumic relaxation and on the rapid ventricular filling. Ventricular relaxation can be affected by various factors such as myocardial fiber stiffness; anomalies in the transportation of intracellular calcium within the myocardial fiber wall, essential in the contraction of the LV fibers (myocardial ischemia disrupts this transportation); and anomalies in the atrioventricular (AV) synchronization, as occurs in the AV block.

Ventricular compliance, unlike ventricular compliance, is a passive process that does not require energy and has an influence in all diastolic phases. Factors that contribute to alter the LV stiffness are myocardial infiltrative diseases (amyloidosis, hemochromatosis, etc.); diseases defined by the own stiffness of the cavities, which cannot normally expand or contract (dilated or hypertrophic cardiomyopathy); or pericardium anomalies that do not allow LV expansion (constrictive pericarditis or cardiac tamponade). Other aspects that affect diastolic function are heart rate and mitral valve anomalies. In tachycardia, the diastole is shortened in a way that the rapid ventricular filling stops, there is no diastasis, and ventricular filling will practically depend on the atrial contraction. Mitral stenosis, for its part, alters significantly the rapid ventricular filling and diastasis.

Entities that cause anomalies in the diastolic function

Diastolic dysfunction can be secondary to multiple heart or systemic diseases. The most frequent causes are hypertension, myocardial ischemia and hypertrophic cardiomyopathy. Hypertension is one of the factors that most influences diastolic function and heart failure. The increase in systemic vascular resistance sets a difficulty at emptying the LV, which causes an increase in ventricular stiffness and consequently hypertrophy. It has been described that there are anomalies of the diastolic function in up to 25% of asymptomatic
hypertensive left ventricular diastolic function using magnetic resonance imaging

Hypertensive patients without ventricular hypertrophy and in 90% with hypertrophy.16

Diastolic dysfunction can also be found in patients with coronary disease. In an acute myocardial infarction there are anomalies of the myocardial metabolism, of ATP consumption and calcium transportation in the myocyte, all causing a delay in contraction.13,14 The influence of other factors that might be present in these patients such as the asynchronicity of the LV, dysfunction of the papillary muscles or mitral valve failure will contribute, to a large extent, to a greater abnormal diastolic function. In this sense, nearly 60% of patients with acute myocardial infarction present with diastolic dysfunction. There are also late complications, as it occurs in cases of LV remodeling, which lead to an increase in ventricular stiffness and consequently to a more abnormal ventricular filling.13–15

Hypertrophic cardiomyopathy is the paradigm of diastolic dysfunction caused by changes in the elastic properties of the myocardium and ventricular stiffness secondary to the increase of myocardial mass, to changes in myocytes, and to LV interstitial fibrosis.17

Valve anomalies disrupt the diastolic function in various ways. In aortic or mitral valvular dysfunction, there are anomalies in the heart chambers with dilation and LV hypertrophy.

Pericardial diseases (constrictive pericarditis) as well as systemic diseases (amyloidosis, sarcoidosis, Fabry disease, hemochromatosis, etc.) also have an influence in the diastolic function due to the infiltration of the myocardium and stiffness increase (restrictive myocardiopathies) (Table 1).

It is common to observe moderate anomalies to the diastolic function in older patients. This is a "physiological" finding since the older, the bigger the myocardial mass becomes and there are changes in ventricular elasticity. Logically, other frequent factors also usually add up in this group of age such as arterial hypertension, cardiac ischemia or anomalies of the cardiac rhythm.13–15

Measurement of the diastolic function using magnetic resonance

Transthoracic echocardiography is the common method to perform routine analysis of the diastolic function (Fig. 2). Pulsed Doppler of transmural and pulmonary venous flow as well as tissue Doppler of the mitral annulus is used.18–21 Similarly, magnetic resonance imaging (MRI) obtains velocity and flow curves through the mitral valve and pulmonary veins, using velocity flow sequences or phase-contrast sequences.18 It has been proved that MRI is reproducible and accurate, with an excellent correlation with transthoracic echocardiography.12–14

After obtaining the localizer at different planes, a standard study is performed obtaining images in the cardiac planes and in cine mode in order to calculate the LV systolic function and anatomically locate the structures where measurements are going to be performed, such as the pulmonary veins and the mitral annulus.19

In our hospital, transmural flow velocity curves are calculated with phase-contrast sequences using retrospective ECG gating (TR: 4.2–7 ms; TE: 2.5–3.2 ms; flip angle: 15–30°; slice thickness: 5–10 mm) in a breath hold, acquiring 40–50 phases per cardiac cycle. Velocity encoding is set at 90–120 cm/s for the mitral valve and 50–80 cm/s for the pulmonary veins to prevent the aliasing.19,21,25 Additionally, another similar sequence is repeated, but the patient is asked to perform Valsalva maneuvers during image acquisition, and to force breathing with closed lips. This sequence allows calculating velocity curves reducing the pressure in the right atrium since the Valsalva maneuver decreases the ventricular preload. In normal subjects, this sequence will show a proportional reduction of the ventricular filling velocity. Its usefulness will help to demonstrate, in some cases, the degree of diastolic dysfunction, as it will be shown later on.19

Sequences are acquired on the mitral valve and the pulmonary vein, preferably on the right superior pulmonary vein, since it has a more constant morphology and caliber, and perpendicular to the infow (through-plane). Regarding the mitral valve, sequences are planned parallel to the mitral annulus, at leaflet level, at the moment of their

<table>
<thead>
<tr>
<th>Table 1 Causes of diastolic dysfunction.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common causes (in order of frequency):</td>
</tr>
<tr>
<td>- Ischemic heart disease</td>
</tr>
<tr>
<td>- Hypertension</td>
</tr>
<tr>
<td>- Age</td>
</tr>
<tr>
<td>- Obesity</td>
</tr>
<tr>
<td>- Aortic stenosis</td>
</tr>
<tr>
<td>Other causes:</td>
</tr>
<tr>
<td>- Myocardial anomalies:</td>
</tr>
<tr>
<td>- Myocardial diseases:</td>
</tr>
<tr>
<td>- Infiltrative diseases: amyloidosis, sarcoidosis, fatty infiltration, thyroid diseases, acromegaly, other restrictive cardiomyopathies</td>
</tr>
<tr>
<td>- Non-infiltrative diseases: idiopathic myocardial hypertrophy and myocardial hypertrophy</td>
</tr>
<tr>
<td>- Endocardial diseases: hypereosinophilic syndrome</td>
</tr>
<tr>
<td>- Metabolic storage disorders: glycogen storage disease, hemochromatosis, Fabry disease</td>
</tr>
<tr>
<td>- Pericardial diseases: constrictive pericarditis, cardiac tamponade</td>
</tr>
</tbody>
</table>

Figure 2  Normal echocardiogram. Transmural flow velocities are shown. The E wave is higher than A wave (E > A).
atrial contraction, which causes a reflux toward the pulmonary veins, which lack valves (it would coincide with the A wave of the transmitral flow). Other additional parameters can also be calculated such as the deceleration time (DT) and isovolumic relaxation time (IVRT). The DT is calculated by drawing a vertical line from the peak of E wave to the "baseline" of the graph (line 1) and a second line from the peak of E wave following the downslope until intercepting with the "baseline" (line 2). The DT is the difference between time line 2 and time line 1. The IVRT is calculated from the time when the aortic valve is closed, shown by the systolic flow in the transmitral graph (reversed flow) until the beginning of wave E (Fig. 5).

Patterns of diastolic dysfunction

With the graphs obtained of the transmitral flow and the pulmonary veins we can assess anomalies in the diastolic function that can be classified as follows (Fig. 6).\textsuperscript{19,21}

Normal pattern (E > A)

In normal subjects, the transmitral flow graph shows a E wave higher than A wave, due to the flow of "rapid filling" (immediately after the opening of the mitral valve). A wave is lower because atrial contraction does not contribute much to the filling. If velocity ratios are calculated, a patient with normal diastolic function has an E/A ratio > 1 (E > A).

Type I: Abnormal LV relaxation pattern (E < A)

During the first stages of the diastolic dysfunction, abnormal relaxation of the LV fibers occurs that reduces the ventricular filling capacity at the first diastolic phase (early rapid filling E wave). This problem is compensated by raising the flow during atrial contraction, that is, the velocity of A wave rises. In the graph, A wave is higher than E wave, with an E/A ratio < 1 (E < A). In the graph of the pulmonary veins, a decrease of D wave occurs. The DT and IVRT become more prolonged because the ventricle needs more time to relax.

This pattern is most common in patients aged over 65 years. Anomalies in LV relaxation, secondary to loss of elastic fibers in its wall, diminishes the "suction" capacity during the isovolumic phase, and, with that, the flow through the mitral valve during the period of rapid filling. The elongation of IVRT and DT translates into a decrease of the AV pressure gradient. This pattern can be also observed in patients with ventricular hypertrophy, hypertension and ischemic heart disease (Fig. 7).

Type II: Pseudonormal pattern (E > A)

As the abnormal ventricular relaxation and rapid ventricular filling progresses, pressure of the left atrium rises as a compensatory mechanism to fill the ventricle. This phenomenon entails a rise of the transmitral pressure gradient (the difference between the left atrium and ventricle) and, with that, an improvement of the rapid filling of the LV that will achieve a rise of E wave in the transmitral graph (E > A). In this phase, thus, a graph of transmitral flow will be obtained.

**Figure 3** (A) Transmitral flow using MR imaging. Sequences are planned (perpendicular to the flow) at the maximum opening of the mitral valves, in four-chamber sections and at the vertical long axis of the LV (arrows). (B) Pulmonary venous flow using MR. It is planned on the axial and coronal planes of the localizer. It is recommended to perform it on the right superior pulmonary vein (lines), approximately 1 cm to the ostium of this vessel (arrows).
Figure 4  (A) Analysis of transmitral flow in a normal subject. A ROI is drawn at the mitral opening or following the contour of the endocardium. Practically the entire ventricular filling occurs during the first phase or "rapid filling" and therefore the E/A ratio will be >1 (E > A). (B) Analysis of pulmonary venous flow in a normal subject. A ROI is drawn at the vessel area to obtain the velocity-time or flow-time curve. The S wave occurs during ventricular systole and the D wave during diastole. The A wave has a negative sense since it is due to atrial contraction.
similar to that of a normal patient (E > A), even though the patient has a diastolic dysfunction. As a consequence, this pattern is called “pseudonormal”.

In order to differentiate between the normal pattern and the “pseudonormal”, the transmitral flow must be measured using the Valsalva maneuver. Under normal circumstances, the Valsalva maneuver will cause a reduction proportional to the velocity of E and A waves, since it reduces the arrival of the blood through the vena cava to the right cavities and, therefore, to the LV, but the E/A ratio is maintained >1. However, in cases of “pseudonormal” dysfunction pattern, the Valsalva maneuver causes the E wave to decrease more, which transforms the graph into a dysfunction pattern type I (E < A). Therefore, it is also very useful to obtain curves of the pulmonary veins because they help detect this “pseudonormal” phase when the D wave is higher than the S wave (Fig. 8).

During this phase of diastolic dysfunction, patients may report exertional dyspnea, secondary to increased atrial pressure. A dilation of the left atrium can even be observed.

**Types III and IV: Restrictive reversible and irreversible pattern (E >> A)**

At this point in time, there is a serious change in ventricular elasticity and relaxation, which leads to a higher pressure within the atrium. This rise of intra-atrial pressure causes the early opening of the mitral valve and the IVRT is

**Figure 5** Transmitral velocity–time curve. The first negative curve is due to the left ventricular (LV) outflow (systole). The second curve, positive, represents the E wave, which is produced by the flow through the valve immediately after the opening of the mitral valve (rapid ventricular filling). The last curve is the A wave, which represents the late filling of the LV by atrial contraction. The isovolumic relaxation time (IVRT) is calculated from the moment when the aortic valve closes, represented by the end of the systolic wave (first negative wave), until the beginning of the E wave. DT (deceleration time) is the time between the vertical intersection of the E wave with the baseline, and the intersection of the downslope of wave E with the baseline.

**Figure 6** Diagram of the transmitral flow (A), with Valsalva maneuvers (B) and pulmonary venous flow (C). In a normal subject the E/A ratio is slightly higher than 1. When there is abnormal ventricular relaxation, the E/A ratio is < 1 and the pulmonary venous flow shows a decrease of the D wave without noticeable changes during the Valsalva maneuver. As the anomaly in ventricular relaxation progresses, the filling pattern changes to a type similar to a normal curve, but with the Valsalva maneuver it changes to a type I pattern (pseudonormal pattern). When the diastolic function becomes more abnormal affecting distension or “compliance” of the LV, the E/A ratio is > 1.5 (restrictive pattern) and in the pulmonary flow graph a decrease of the systolic flow and a rise of the diastolic D wave (S < D) can be observed. If variations occur with the Valsalva maneuver, the pattern is considered restrictive reversible; otherwise, it would be irreversible.
If Valsalva maneuvers are used and a change in the filing pattern is observed toward a type I or II of the diastolic dysfunction, it is said that the restrictive pattern is reversible (Fig. 9). On the contrary, the restrictive pattern is irreversible or grade IV, when the pattern persists despite using Valsalva maneuvers.

The restrictive pattern is typical of restrictive cardiomyopathies (amyloidosis, sarcoidosis, hemochromatosis, etc.), of dilated cardiomyopathies with depressed systolic function, and of constrictive pericarditis.

At this point, patients frequently show symptoms and signs of congestive heart failure. The rise of intra-atrial pressure will cause a significant increase in size of the left atrium.

Limitations

The measurement of the diastolic function based on the calculation of velocity curves of transmitral and pulmonary vein flow has limitations that are necessary to be aware of, since it depends on compliance and relaxation of the LV, LV filling pressure, preload, valvular diseases, cardiac rhythm and arrhythmia. The most important limitations occur in cases of preload reduction (or rise of afterload) since it will cause a decrease in E wave and can be confused with a type I dysfunction pattern. Moreover, an increase of pressure in the right ventricle (RV), as it can occur in pulmonary thromboembolism or in RV infarction, can affect the curves and lead to a pattern of abnormal LV relaxation (type I). In cases of tachycardia, a shortening of the diastole can cause a rise in E wave or even a fusion of both waves making it difficult to define the type of diastolic dysfunction pattern. In patients with atrial fibrillation, a reliable curve cannot be obtained since there is no atrial contraction and E wave will not be drawn. Regarding valvular diseases, studies can also be limited. In severe mitral insufficiency, atrial pressure is very high and the regurgitation flow shortens the LV rapid filling which leads to a restrictive type curve.

Other forms of measuring the diastolic function

Tissue Doppler

Like in echocardiography, a ROI is placed at the mitral annulus in the four-chamber plane. A curve with negative waves on the baseline is obtained, with a first wave which will be called E or e', and a second wave A or a'. This measurement can also be obtained using MR imaging, with phase-contrast sequences, in a way similar to the one obtained for the transmitral flow and pulmonary venous flow. In this case, the ROI is placed at the myocardial muscle, normally using a short axis in the mid plane and at the inferoseptal segment, in order to spread it along all images of the cardiac cycle. It must be taken into account that velocity must be set at around 30 cm/s. This measurement reflects the degree of myocardial shortening and provides information regarding the relaxation degree, which is not affected by the aforementioned limitations of the transmitral flow measurements, mainly preload anomalies, atrial fibrillation or tachycardia and valvular disease. In this sense,
Figure 8  Pseudonormal pattern. Patient with ischemic heart disease and ejection fraction of 55%. The analysis of the transmitral flow reveals a E/A ratio > 1, suggesting a normal diastolic function (left image). However, when the analysis is performed using the Valsalva maneuver the E/A ratio is < 1. These findings are typical of a pseudonormal pattern (type II pattern of the diastolic dysfunction).

Figure 9  (A) Patient with dilated cardiomyopathy with slightly depressed systolic function with EF of 43%. (B) The analysis of the transmitral flow shows diastolic dysfunction with a restrictive pattern defined by an E > A ratio. (C) A slight variation in velocities can be observed when the transmitral flow is analyzed using the Valsalva maneuver, showing that the restrictive pattern is reversible (pattern type III). (D) The pattern of flow the pulmonary veins (red line) and the vena cava (green line) show a S wave < D since the pressure gradient between the pulmonary veins (or vena cava) and the left atrium (or right atrium) is reduced due to increased atrial pressure.
it is a method of great help to distinguish a "pseudonormal" pattern. An E/e' ratio < 10 is considered normal (Fig. 10).

Size of the left atrium

As already mentioned, as the diastolic dysfunction degree increases, there is also an increase of the left atrial pressure that leads to a size increase. Increased left atrial size indicates chronic diastolic dysfunction and, therefore, is a good marker, not only of the time of diastolic dysfunction, but also of its seriousness. However, it has its limitations, since it can also be increased due to other processes, fundamentally valvular diseases. Therefore, the possibility of diastolic dysfunction must be confirmed by using this method in absence of valvular disease. The size of the left atrium can be measured using four-chamber planimetry at the end systolic phase, just before the opening of the mitral valve, which is when the atrium reaches its largest size. An area > 20 cm² indicates increased atrial size, which becomes serious when it exceeds 40 cm². Calculating the volume is a more complex process. Two projections are required, normally a long-axis and a four-chamber projection.21,28-30

Myocardial tagging

It is obtained using saturation bands, which allow visualization of the degree of myocardial deformation during the cardiac cycle. It is measured using deformity or torsion units. The torsion degree is known to be an important factor in ventricular function. This type of movement is due to the endocardial oblique fibers that contribute to the effectiveness of the myocardial contractility and relaxation. However, measurements take a long time and require great expertise, which has limited its routine use.31

Spectroscopy

Spectroscopy using 30P-MR imaging allows measurements of the myocardial phosphocreatine and adenosine
triphosphate (ATP). The PCR/ATP ratio shows the energy state of the cardiac muscle. A decrease in the ratio indicates a state of high energy and can be a marker for diastolic dysfunction in patients with arterial hypertension or left ventricular hypertrophy. As with the previous method, it requires long sequences and great expertise, reason for which it is not used routinely.\textsuperscript{21}

Conclusion

Diastolic dysfunction is a common cause for congestive heart failure in the absence of valvular heart disease with normal systolic function. It must be considered as a continuous process that begins with relaxation anomalies and evolves to an irreversible restrictive state. Not all patients will progress in such a linear way, since detection at early stages, as it may occur in hypertensive patients, can facilitate its regression with appropriate treatment. For this reason, it is conceptually important to determine the degree of severity of the diastolic dysfunction, so it must be yet another parameter of information when a MR cardiac study is performed. The use of phase-contrast sequences to assess transmial flow and pulmonary venous flow is a simple method that requires very little additional time, since it can be performed in a single breath hold.

Authorship

1. Responsible for the integrity of the study: GCFP and RD.
2. Conception of the study: GCFP, RD, JC and JSG.
3. Design of the study: GDFF, MCC and JSG.
4. Acquisition of data: GCFP, RD and JC.
5. Analysis and interpretation of data: GCFP, JSG, JC and MCC.
6. Statistical analysis: GCFP, JC and JSG.
7. Bibliographic search: RD, GCFP and MCC.
8. Drafting of the paper: GCFP and MCC.
9. Critical review with intellectually relevant contributions: MCC, JC and RD.
10. Approval of the final version: GCFP, RD, MCC, JC and JSG.

Conflicts of interest

The authors declare not having any conflict of interest.

References

24. Karwatowski SP, Brecker SJ, Yang GZ, Firmin DN, Sutton MS, Underwood SR. Mitral valve flow measured with cine MR velocity mapping in patients with ischemic heart disease: