Evaluation of Diastolic Function: How Practical Is it?

Moderated by Philip R. Liebson, MD
Discussants: Rami Doukky, MD; Melissa Tracy, MD

**DR. LIEBSON:** I am Dr. Philip Liebson from the Section of Cardiology, Rush University Medical Center, Chicago. I am joined today by two of my colleagues from the Section of Cardiology and Echocardiography: Dr. Rami Doukky, Associate Professor of Medicine, Radiology and Dr. Melissa Tracy, Associate Professor, Cardiology, both of whom have been very active in the area of echocardiography.

The topic for discussion is “Evaluation of Diastolic Function, How Practical Is It?” and encompasses an area in which there has been much research and, I have to admit, much confusion. If you have seen the report of an echocardiogram on one of your patients with the information on diastolic function, indicating “impaired relaxation,” “pseudo-normal function,” or “reversible or fixed restrictive dysfunction,” you may have wondered what it means, especially when accompanied by a normal left ventricular ejection fraction (LVEF). We will consider the importance of these findings and the role of diastolic dysfunction and diastolic heart failure in the management of cardiac patients, especially when systolic function is considered to be normal. We will also discuss some of the more recent advances in the evaluation of diastolic function in echocardiography and other noninvasive measurement.

Let’s start out with the question, what is the importance of diastolic function?

**DR. DOUKKY:** Diastolic function assessment sheds light on left ventricular (LV) performance beyond systolic function. Clinicians are often fixated on the EF, which is certainly important and many of our management decisions are based on it. However, cardiac function is not completely summed up in the EF. A good deal of information about contractility could also be assessed by other means such as myocardial strain, but this is not the subject of our discussion today.

Diastolic function assessment, on the other hand, provides additional insight, particularly in symptomatic patients. It helps us better understand the physiology in patients with normal or impaired systolic function by providing additional information regarding the loading condition of the patient, i.e., the LV filling pressure. It also provides valuable prognostic information beyond EF.

**DR. LIEBSON:** Dr. Tracy, what is the difference between the terms diastolic dysfunction and diastolic heart failure? Is there an important difference?

**DR. TRACY:** I would like to echo a couple of points that Dr. Doukky stated. The reason why we need to discuss diastolic function on every echocardiogram is that diastolic dysfunction (abnormal filling/relaxation) is present in virtually all patients with heart failure. In addition, 50% of patients who are admitted for congestive heart failure (fluid overload) actually have...
normal LVEF, ie, normal pumping function to their heart, but abnormal diastolic function coupled with signs and symptoms of heart failure, ie, diastolic heart failure.¹

If the echocardiogram comes back and the referring physicians read “normal systolic function or normal LVEF” with no mention of diastolic function, they may immediately think that this patient does not have any issues regarding the filling/relaxation of the heart and/or cardiac etiology for the heart failure symptoms, which would be incorrect. If we avoid and ignore the fact that there are both systolic (pumping) and diastolic (filling) physiological factors working together for hemodynamic stability as well as other parameters such as those in a physical exam, chest radiograph, and biomarkers, we may actually not treat our patients appropriately. These patients will definitely have progression of disease with admissions/readmissions for heart failure and a worse risk of mortality. Recently, an article in the Journal of Cardiovascular Translational Research identified several biomarkers in the plasma, which can be measured. These biomarkers included brain natriuretic peptide and markers of collagen homeostasis and fibrosis. Since there are several etiologies leading to diastolic dysfunction, it would be a reasonable conclusion that multiple biomarkers used independently and in combination will need to be followed to better diagnose, treat, and improve outcomes for patients with diastolic dysfunction.

Looking at all of the parameters of an echocardiogram for diastolic function is important. The difference between diastolic dysfunction and diastolic heart failure is that the latter presents with signs and symptoms consistent with heart failure in the absence of depressed LVEF. There are 4 different levels of diastolic dysfunction.

Therefore, what you were alluding to in your first statement, Dr. Liebson, is that we use these scientific words, but we don’t really know what they mean. I think it is important that the referring physicians understand that there are 4 different stages of diastolic dysfunction, and a patient can actually fluctuate between stage 1 to stage 3, but stage 4 tends to be irreversible.

Stage 1 is a mild form of diastolic dysfunction. At this stage, if, for example, the patient’s blood pressure is treated well, he/she may be able to prevent the level of diastolic dysfunction from progressing. Stage II, is called pseudonormal and is a moderate degree of diastolic dysfunction. Stage III and IV are severe forms of diastolic dysfunction, with stage IV typically being irreversible. Therefore, diastolic dysfunction is a big problem, and it is very important that we have discussions, so that when the referring physician gets the echocardiogram, he/she understands the verbiage.

Dr. Liebson: I have to emphasize that diastolic dysfunction and isolated diastolic dysfunction are quite common, especially in the elderly, and there are population studies to indicate that at least half of the elderly with heart failure have LVEFs greater than 45%, and in some studies, diastolic heart failure is present, apart from systolic heart failure, in up to 75% of elderly patients.

Dr. Doukky: I would like to elaborate on Dr. Tracy’s remarks. Heart failure is a clinical diagnosis manifesting with well-known signs and symptoms. This should not be confused with diastolic dysfunction, which is an echocardiographic finding not necessarily associated with clinical heart failure syndrome.

It is not unusual for some to confuse diastolic dysfunction with diastolic heart failure. When patients with preserved systolic function present with classic symptoms of heart failure, they are usually at more advanced stages of diastolic dysfunction, manifesting as diastolic dysfunction grade 2, 3, or 4 on echocardiography.

I agree with Dr. Liebson that the prevalence of diastolic heart failure is increasing among the elderly, especially at the community level. In referral centers, we tend to see more patients with systolic heart failure. At the community level, nonetheless, diastolic heart failure is certainly on the rise, particularly in the elderly. In our lifetime, diastolic dysfunction with preserved EF will probably be the most common cause of heart failure.

Dr. Liebson: In every type of evaluation, you need to have a gold standard, and I would like to ask what we consider the gold standard to be for the evaluation of diastolic function.

Dr. Tracy: The gold standard would definitely be echocardiography.

Dr. Liebson: Can echocardiography be compared to another standard, which may be more direct? That really is the thrust of my question.

Dr. Doukky: The “tau”, which can be measured with left-heart catheterization, is widely accepted as a standard invasive indicator of the rate of LV relaxation, while catheter-measured LV end-diastolic pressure is the gold
I think differentiating diastolic function. I definitely want to echo what Dr. Doukky has said, that diastolic dysfunction is not a diagnosis that you can make at the bedside.

If you have a patient who does not have a history of systolic dysfunction or a weak heart muscle and is admitted with heart failure, the echocardiogram helps you decide whether the patient has systolic dysfunction, diastolic dysfunction, or a combination of systolic and diastolic dysfunction or heart failure and whether you need to look at possible pulmonary issues.

So, echocardiography is really paramount in being able to diagnose a patient's condition correctly.

To diagnose diastolic dysfunction, you definitely have to look at many different parameters. You have to look at what is called the mitral valve inflow while looking at the pattern and ratio between early (E) and late (atrial, A) ventricular filling velocities (E/A ratio), tissue Doppler obtained on a standard echocardiogram for every patient.

Pulmonary vein flow is not easy to measure in patients because you need the sample volume of the echocardiogram at least 1 to 2 cm within the orifice of the pulmonary vein, and I like to try to get more than one pulmonary vein if possible, as the information that you can get on pulmonary vein flow is really helpful.

I then look at pulmonary pressures and see if they are elevated. I also check the left atrial size and left atrial indexed volume. All this should be obtained on a standard echocardiogram for every patient.

I then examine these parameters to see where one parameter is indicates diastolic dysfunction. So, it's not just one index that you should consider for diastolic dysfunction. You have to examine these individual parameters for each patient to decide where the patient is fitting. If you consider all of these different indices, you will have a good way of diagnosing a patient with either normal diastolic dysfunction or the range of diastolic dysfunction.

standard for assessing the filling pressure. Certainly, no one uses these invasive tools for the routine assessment of diastolic function. Therefore, the practical gold standard remains echocardiography, which can reliably assess the state of diastolic function and the filling condition of the patient in the vast majority of the cases. Occasionally, conflicting diastolic indices may limit our ability to evaluate diastolic function echocardiographically. In such situations, invasive assessment is still an option.

**DR. TRACY:** In general, a lot of our measurements are based on cardiac catheterization, but if you look at the last 10 years, the amount and reproducibility of data that we can get from an echocardiogram allow you to evaluate filling parameters, valvular dynamics, and pressure gradients from the noninvasive and highly reproducible echocardiogram and compare it to the invasive cardiac catheterization.

We refer back to cardiac catheterization, but in the last 10 years, the area of echocardiography has exponentially grown to the point that you will have an invasive cardiologist and/or a surgeon come to echocardiography laboratory asking the echocardiographer to assist him/her with a particular case based on the findings from the echocardiogram. This is because, as Dr. Doukky mentioned, the information does not always fit together perfectly like a puzzle, so there are many different findings on the echocardiogram that should be looked at for classification of a patient's report as normal or abnormal. If the echocardiogram is not normal, then where does the patient fit in the paradigm of diastolic dysfunction?

If you only focus on the mitral valve inflow or the tissue Doppler alone in a vacuum, you will have a difficult time accurately diagnosing diastolic dysfunction. Normal LVEF with abnormal systolic function. We could discuss further about whether that it is still feasible/appropriate, but for the purpose of this discussion, if an echocardiogram within approximately 12 hours of admission demonstrates an EF of 50% or greater, one should evaluate diastolic dysfunction.

To diagnose diastolic dysfunction, you definitely have to look at many different parameters. You have to look at what is called the mitral valve inflow while looking at the pattern and ratio between early (E) and late (atrial, A) ventricular filling velocities (E/A ratio), tissue Doppler obtained from the mitral valve annuli, also to review the E/e prime ratio, and the pulmonary vein flow, which I have found to be extremely helpful.
DR. LIEBSON: Dr. Doukky, do you have any further comments about this?

DR. DOUKKY: I agree with Dr. Tracy. You have to look at all indices. I also make an effort to not only specify the stage of diastolic dysfunction but also comment on whether the LV filling pressure is elevated or not, as it may explain the patient's dyspnea, for example. On the clinical level, knowing whether the patient is volume overloaded or not is most useful for the managing physician.

DR. LIEBSON: Different patients obviously have different issues other than the diastolic pressure, but are there any situations where it may be difficult to assess diastolic dysfunction using echocardiography?

DR. DOUKKY: Yes, there are situations where it is relatively difficult to interpret diastolic function. In atrial fibrillation, for example, the loss of the atrial contraction limits our ability to assess E/A ratio and changes the pulmonary vein flow pattern. In this case, I find the E/e’ ratio to be very useful. A high ratio still identifies high LV filling pressure, which is most important clinically. Secondly, the absolute e’ velocity provides a useful assessment of LV diastolic relaxation, independent of the loading condition of the patient. In addition to atrial fibrillation, sinus tachycardia represents a similar challenge.

DR. LIEBSON: I think it’s important that the e’, or the filling, based upon the mitral annular motion in early diastole, is not heart-rate dependent, and the ratio of E/e’ may be very important in atrial fibrillation, where, if you could determine the mitral inflow E and the e’ of the mitral annulus at the same time, you could obtain some valuable information about filling pressures.

DR. TRACY: I would like to add to Dr. Doukky’s point. The echocardiogram can also be difficult to interpret in patients who have body habitus issues and chronic obstructive pulmonary disease or those with tachycardia accompanied by extreme shortness of breath. Thus, both atrial fibrillation, where you have to take an average of at least 10 cardiac cycles, and tachycardia, where the E and A wave can be fused, make it difficult to examine and use the echocardiogram parameters.

In order to ensure that our referring physicians do not get frustrated, we have to remember that not only has the patient beautiful echocardiographic windows, and we may want to look at other parameters if that patient has a difficult body habitus and bad chronic obstructive pulmonary disease, or if the patient is technically unable to withstand an echocardiogram. I just want to preface that because we still may have technically limited studies.

DR. LIEBSON: Suppose we have the results of the echocardiography and they show that there is a diastolic relaxation abnormality and evidence of diastolic dysfunction, while the systolic function is normal. The next question that arises is what sort of intervention is required. In other words, how does the indication that there is diastolic dysfunction affect treatment?

DR. DOUKKY: I think it comes down to a couple of issues: one is whether there is high LV filling pressure, and second, whether the patient is symptomatic. In symptomatic patients, evidence for elevated LV filling pressure, often seen in grade 2 or 3 diastolic dysfunction, can actually explain the patient’s symptoms. In such a case, treatment with diuretic can relieve the patient’s symptoms. Additional interventions, such as angiotensin II receptor blockers (ARBs), may improve the associated morbidity and lower hospital readmission rate as has been shown in the Effects of Candesartan in Patients with Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM-Preserved) trial.\textsuperscript{9}

Another important piece of information is whether the patient has restrictive filling pattern and whether it is reversible. Irreversible restrictive filling pattern after diuretic treatment or the Valsalva maneuver carry very poor prognostic implications and such a patient may be considered for a heart transplantation.

On the other hand, echocardiographic findings of preserved systolic function and grade 1 diastolic dysfunction without evidence of elevated filling pressure carries a good prognosis and may simply represent relaxation abnormality associated with the normal aging process. However, grade 1 diastolic dysfunction in patients younger than 60 years of age may represent impaired relaxation most commonly caused by long-standing hypertension and may be a precursor to more advanced diastolic impairment. In the latter case, no specific intervention other than addressing the underlying condition, such as hypertension, is needed.

Occasionally, we encounter what some call grade 1B diastolic dysfunction, which is when you have a relaxation abnormality manifesting as reversal of E/A ratio, but along with that, you have evidence for elevated LV filling pressure demonstrated by an increased E/e’ ratio. You can think of this as a transitional phase between diastolic dysfunction grades 1 and 2. This may be associated with heart failure symptoms, which may improve with diuretics.

DR. LIEBSON: Dr. Tracy, do you feel that there are certain classes of pharmacologic agents that might be more helpful in patients with diastolic dysfunction?

DR. TRACY: The data at this point do not support one specific form of a
medication that is going to be the most beneficial. Obviously, angiotensin-converting enzyme (ACE) and ARBs, beta-blockers, and diuretics are paramount. The problem with diastolic dysfunction is that we have actually not been able to treat diastolic dysfunction as well as we would like to.

Patients diagnosed with diastolic heart failure actually portend a poor prognosis. One reason may be that we do not treat it as aggressively and as early as we should. It could also be that we think we have to focus on patients with systolic dysfunction and make sure that their blood pressure is better and under control and that their fluid status is tighter.

But the diastolic dysfunction patient actually portends a worse prognosis. I think it is important that when we encounter a patient with grades 1, 1A, or 1B diastolic heart failure, the referring physician must establish that the patient does not have a previous history of diastolic dysfunction and that they are not currently being treated for blood pressure. For this patient, the mild blood pressure must be monitored and the physician must check if maybe diet, exercise, and losing weight would control the blood pressure better.

If the condition has taken a toll on the heart muscle and is no longer just isolated elevated blood pressure, but also shows signs of early diastolic dysfunction, then you need to be aggressive with that patient’s treatment to be able to control the blood pressure.

I have had female patients who I have performed echocardiography for while they were pregnant. I would perform an echocardiography for them for tachycardia and for diagnosing grade 1 diastolic dysfunction. I have actually been performing an echocardiography on such patients 6 months post-partum because the diastolic dysfunction showing on a baseline echocardiogram may be a marker of diastolic dysfunction that is going to develop in these patients.

So, I repeat the echocardiography to see if the earlier findings are just a normal physiologic response to pregnancy or an early marker of what’s to come. With diastolic dysfunction, as Dr. Doukky said, I also use ACE inhibitors, ARBs, and diuretics. Those have been shown to be our best therapeutic interventions for diastolic dysfunction.

**DR. LIEBSON:** I would just like to add an overview on various types of agents. With regards to diastolic stiffness, especially involving the LV, the only current therapy with a salutary effect on vascular and ventricular stiffness that leads to reduced smooth muscle growth, reduced growth factor expression, and regression of myocardial fibrosis consists of the class of ACE inhibitors. There is evidence that ARBs and aldosterone receptor antagonists may also have efficacy in decreasing myocardial fibrosis and thus diastolic dysfunction. Beta-blockers and certain calcium channel blockers (verapamil and diltiazem) may also be helpful by prolonging diastolic filling time.10–15

ACE inhibitor therapy, as we know, may result in favorable remodeling of the atrium independent of blood pressure.16

There have been several clinical trials involving patients with heart failure having normal EFs. These include the CHARM-Preserved perindopril trial7 and the Irbesartan in Heart Failure with Preserved Systolic Function (IPRESERVE) trial.7 All of these patients supposedly had normal EF, but the actual EFs were ≥40%. Now, we know that in echocardiography, we consider the normal EF to be >50%, so some of these patients certainly had EFs below what we considered normal.

The diastolic indices in these studies included the intraventricular relaxation time, the E/A ratio, the deceleration time, and the left atrial dimension. The problem was that in all 3 of these studies, there was no evidence that diastolic function had any prognostic significance with the primary outcome, which in these cases, were deaths or heart failure hospitalization. However, there is some evidence in the CHARM-Preserved trial that candesartan, an ARB, significantly reduced hospitalization for congestive heart failure and in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study,18 there was some improvement in symptoms and exercise capacity with perindopril administration.

Statins may have a favorable pleiotropic effect on diastolic function19; statins and beta-blockers in patients with heart failure and preserved LVEF may prevent mortality.12 Statins have been used for heart failure patients using ACE inhibitors, but mostly in patients whose LVEFs have been low.

And finally, there are some interesting studies20,21 showing that sildenafil, which has a phosphodiesterase-5A inhibition effect, may suppress chamber and myocyte hypertro-

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-Melissa Tracy, MD
Dr. Doukky has said, do you feel that Myocardial strain imaging, however, is not affected by the angle-dependency relative to each other. Therefore, it is important as a general adjunct in the echocardiography laboratory or just as a research tool?

**DR. TRACY:** I think that in the next 5 years, if the technology across the vendors can become reproducible, the strain and strain rate could be very valuable. To elaborate a little on what Dr. Doukky was saying, if you only look at mitral inflow or tissue Doppler, there are absolute limitations.

One is age, because we know that beyond the age of 65 years, mitral valve inflow pattern alone becomes less reliable as a tool. We also haven’t talked about the fact that if a patient has a prosthetic valve or a significant amount of mitral annular calcification, tissue Doppler becomes unreliable.

So, I definitely think that the limitation on strain and strain rate indices is due to a few factors. One of the limitations is that the specific indices are not reproducible by all of the vendors. So, we cannot reproduce what one vendor is doing with another vendor’s equipment, and thus, we rely on information that is vendor specific. This results in confusion and bias.

The other limitation is that there is a learning curve with new and evolving technology. In addition, with the currently available equipment, a long time may be required to obtain accurate information. In order to implement strain and strain rate into our everyday workflow, the sonographers, fellows, and faculty must be adequately trained and the time necessary to measure these indices accurately must not be fraught with hindrance and limitations.

**DR. LIEBSON:** Thank you, Dr. Tracy. Just for the sake of completeness, magnetic resonance imaging (MRI) has been used for diastolic dysfunction. Do either of you have any comments about the use of MRI? Not that it would be an everyday procedure, but any comments on the benefit, if any?

**DR. TRACY:** MRI is the ideal method to quantitate LV mass and volume. However, I don’t believe the current technology by means of MRI can surpass what can be assessed by echocardiogram based on scientifically proven measures, reproducibility, timeliness, and cost. Finally, there’s still the issue of patients who cannot undergo MRI because of prosthetic equipment and/or claustrophobia.

The images and the information that are obtained from a cardiac MRI are great, but in my opinion, their use will be more related to research rather than every day clinical practice.

**DR. LIEBSON:** Nonetheless, there is valuable information in certain situations where MRI can provide information on diastolic dysfunction.

**DR. TRACY:** I agree with you completely, Dr. Liebson. Extrapolating your question of where we think MRI may be going in the next 5 years, I remember talking about cardiac computed tomography (CT) and cardiac MRs 20 years ago and thinking that this is a big thing and that echocardiograms were going to become obsolete. I couldn’t have been further from the truth. I do believe that the data obtained from cardiac CT and cardiac MR will also continue to grow, but you are not going to be able to get around the limitations of prosthetic devices. There are newer prosthetic devices (artificial heart valves and pacemakers), which will not be perturbed by the MRI procedure, but we will still have many generations of patients with prosthetics that can’t safely utilize this advanced cardiac imagery.

There are also patients who are claustrophobic. Finally, the way our
Diastolic dysfunction is an important prognostic indicator, especially in patients with normal systolic function. The important thing is that clinicians must know how to interpret the results of echocardiography, which, again, currently is the gold standard, the easiest way to determine diastolic function or dysfunction.

At present, I think the major concern that many clinicians have is that they do not understand what the echocardiographic findings mean, and it is extremely important for the echocardiographers to educate their clinicians, so that they know how to interpret the echocardiographic report. Nonetheless, there will be some excellent, important, new findings in echocardiography over the next few years. We have touched upon some of them, and I feel echocardiogram will remain an important procedure for evaluating cardiac function, especially in diastole.

Clinical Implications

» Distinguishing between diastolic heart failure and systolic heart failure is important because of the differences in treatment and prognosis.

» In some studies, over 50% of patients who are admitted for congestive heart failure actually have normal systolic function.

» Diastolic dysfunction is an important prognostic parameter, especially in patients with normal systolic function.

» Atrial fibrillation makes it difficult to diagnose diastolic dysfunction because of the loss of atrial contraction that limits the E/A ratio and changes the pulmonary vein flow profile.

» Angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, beta-blockers, and non-dihydropyridine calcium channel blockers are possible therapeutic interventions for diastolic dysfunction, but other classes of agents such as aldosterone receptor blockers and phosphodiesterase inhibitors are being investigated.
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