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USE AND LIMITATIONS OF E/E' TO ASSESS LEFT VENTRICULAR FILLING PRESSURE BY ECHOCARDIOGRAPHY

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Measurement of left ventricular (LV) filling pressure is useful in decision making and prediction of outcomes in various cardiovascular diseases. Invasive cardiac catheterization has been the gold standard in LV filling pressure measurement, but carries the risk of complications and has a similar predictive value for clinical outcomes compared with non-invasive LV filling pressure estimation by echocardiography. A variety of echocardiographic measurement methods have been suggested to estimate LV filling pressure. The most frequently used method for this purpose is the ratio between early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), which has become central in the guidelines for diastolic evaluation. This review will discuss the use the E/e' ratio in prediction of LV filling pressure and its potential pitfalls.

KEY WORDS: Left ventricular filling pressure · Echocardiography · Doppler echocardiography.

INTRODUCTION

Heart failure is responsible for a huge burden of disease in both developed and developing countries.[1] Among patients with heart failure, about 50% show normal or preserved left ventricular (LV) systolic function (HFpEF).[2] In the detection and evaluation of heart failure, echocardiography plays a crucial role in evaluation of ventricular systolic function, identification of other structural heart diseases, and hemodynamic assessment, including classification of diastolic dysfunction.

Although the diagnosis of HFpEF is often considered a diagnosis of exclusion, recent European guidelines have focused on the evaluation of LV filling pressure.[3] Moreover, measurement of LV filling pressure also imparts valuable information for decision making and prediction of clinical outcomes. While invasive cardiac catheterization is the gold standard in gauging LV filling pressure, recent echocardiographic studies have identified no difference in outcome between the invasive measurement of filling pressure using the Swan-Ganz catheter and non-invasive echocardiography.[4)5] A number of studies have identified the risks of invasive measurement of LV filling pressure, and it seems likely that the benefits obtained from this information are outweighed by the complications of invasive measurement. In contrast, the echocardiographic method is rapid and non-invasive, and it can be done at a patient's bedside. However, echocardiographic methods can give us unreliable values under various clinical conditions. The purpose of this review is to highlight their strengths and weaknesses.

UNDERSTANDING CARDIAC CYCLE AND DIASTOLIC FUNCTION

Understanding the cardiac cycle and the physiology of LV filling is the basis for interpretation in a comprehensive echocardiographic evaluation of diastolic function. Normal diastolic function is necessary to adequately fill the heart without elevation of in diastolic filling pressure.[6] Ventricular systolic function can be readily measured as the ejection fraction (EF).[7] However, evaluation of the diastolic function is more difficult.[8] The diastolic phase is a well-organized process that enables optimal ventricular filling for a given clinical condition.[9]

The diastolic phase is composed of four phases; isovolumic relaxation, early rapid ventricular filling, diastasis, and atrial contraction (Fig. 1). LV filling is not a passive process.[10] During LV contraction, myocardium is compressed and twisted.[11]

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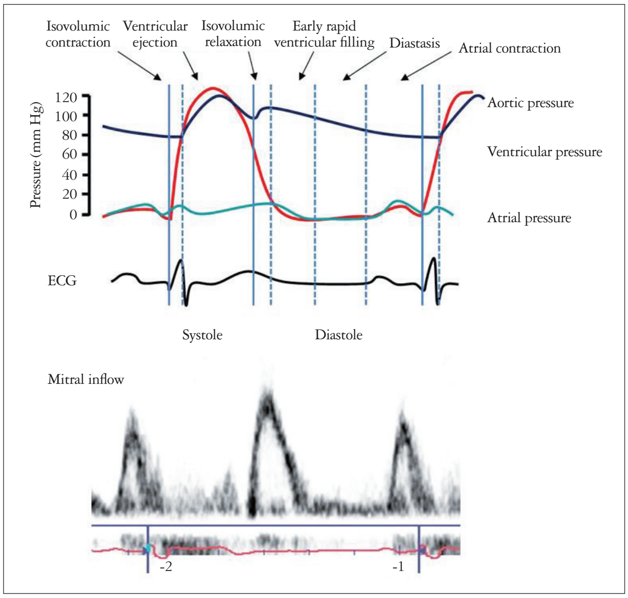

Fig. 1. Diagram of intracardiac pressures according to the cardiac cycle. During diastole, pressure gradient between left ventricle and left atrium derives blood flow.

Relaxation of the myocardial contraction and twist unloads this energy, and this process begins before the end of LV ejection. LV pressure falls rapidly during the isovolumic relaxation period and produces an early diastolic pressure gradient between the left atrial (LA) and LV that sucks blood out of the LA and fills the LV rapidly. Thus, in the normal heart, myocardial relaxation (e') and suction precede the onset of LV passive filling (E). In contrast, the failing ventricle shows reduction of passive ventricular filling and elevation of LA pressure,[12)13)] so blood is pushed rather than sucked into the LV. In this setting, myocardial diastolic motion (e') reflecting cardiac movement during diastole may be secondary to filling (E).[14)] The distinction in the mode of LV filling (and thereby e') explains the different behaviour of E/e' with impaired and preserved LV function.

Echocardiographic methods in the estimation of LV filling pressure

A number of echocardiographic techniques can be used to measure LV filling pressure. Increased LA size on 2-dimensional echocardiography is an indicator of increased LV filling pressure.[15)] The presence of enlarged LA, while non-specific, provides evidence of long-standing elevation LV filling pressure elevation, and LA volume is a more sensitive marker than LA diameter.[16)17)] However, the process of reverse remodelling of the LA may not be rapid, so that LA enlargement may be a legacy of previously increased LV filling pressure.

Mitral inflow velocity (E) correlates well with LV filling pressure in heart failure, but in the broader community, abnormalities are non-linear because the measurement is affected by both myocardial relaxation and filling pressure. Transmitral inflow is proportionate to the ratio between LA pressure and the relaxation time constant, tau, whereas e' is inversely proportionate to tau only, leading the ratio E/e' to be proportionate to LA pressure. The use of E/e' is generally the most a feasible as well as among the most reproducible method for estimation of filling pressure. Several prominent validation studies have confirmed the correlation of this ratio with filling pressure, and the prediction of normal and abnormal filling pressure is most reliable when the ratio is < 8 or > 15.[18)19)] However, the examiner should use these as a combination of other Doppler variables and should check for the presence of other clinical conditions that can influence these variables.[19)20)] Recently, E/e' has been correlated with ambulatory measurement of LA pressure in 60 simultaneous studies, with an area under the receiver operating curve > 0.9.[21)]

The correlation of E/e' with LA pressure compares favorably with the low correlation of LA pressure with type B natriuretic peptide. Moreover, while the correlation of E/e' with LA pressure is best in the setting of impaired LV systolic function, it holds true with preserved systolic function, and despite changes of loading, for example in aortic stenosis and exercise.[22)] Although high heart rates may present a challenge because of fusion of the E and A waves, the relationship appears to hold true in atrial fibrillation. Finally, the measurement of E/e' has been shown to correlate with outcome in patients following myocardial infarction, in aortic stenosis and post exercise.[23)24)]

Pitfalls of E/e'

Despite favorable correlations, some investigators have proposed that the method is an unreliable means of assessing filling pressure. In decompensated advanced systolic heart failure, E/e' showed a poor correlation with intracardiac filling pressures, especially in large LV volumes, worse cardiac indices, and in the presence of cardiac resynchronization therapy.[25)] These results are likely driven by significant mitral regurgitation (present in 22% of the patients) as well as half of the patients with a broad QRS and consequent abnormal septal motion.[21)] The study should remind us of the pitfalls of measuring E/e'.

Technical considerations

The measurement of E velocity is derived from pulsed-wave (PW) Doppler, usually in the apical 4-chamber view. Using color flow imaging is helpful for the optimal location of sample volume of the Doppler beam. A 1-3-mm sample volume is placed between the mitral leaflet tips during diastole. Mitral inflow waveforms can be recorded clearly after optimization of spectral gain and wall filter setting. Mitral inflow velocities should be measured at end-expiration with a higher sweep speed (100 mm/sec) (Fig. 2). Errors may arise from use of inappropriate location, sample volume or respiratory state. Measurements should be averaged over more than three consecutive beats.

Annular pulsed wave Doppler tissue imaging is also obtained from the apical 4-chamber view, using a 1- to 2-mm size sam-

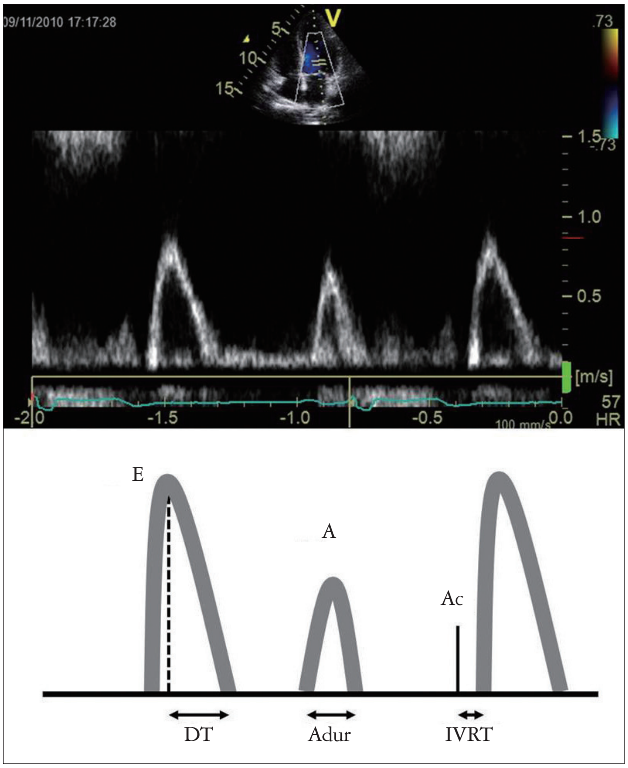

Fig. 2. Mitral inflow velocities obtained by pulsed wave Doppler technique and their schematic diagram. Peak mitral inflow velocity during early diastole (E wave), peak mitral inflow velocity at atrial contraction (A wave), mitral deceleration time (DT), duration of A wave (Adur), and interval between aortic valve closure (Ac) and start of mitral inflow (IVRT) are labelled. IVRT: isovolumic relaxation time.

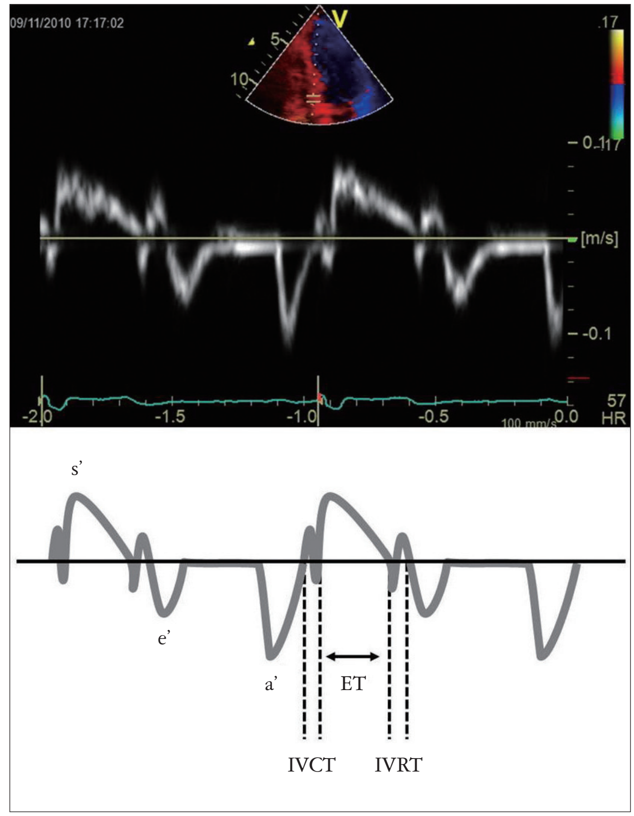

Fig. 3. Mitral annular velocities obtained by tissue Doppler echocardiography. s’ velocity: systolic velocity, e’ velocity: early diastolic velocity, a’ velocity: late diastolic velocity, IVCT: isovolumic contraction time, ET: ejection time, IVRT: isovolumic relaxation time.

ple volume (Fig. 3). Angulation between the ultrasound beam and the plane of cardiac motion should be minimized (< 20°). Averaging of e’ velocity from the septum and lateral side of the mitral annulus is desirable. Errors may arise from excessive Doppler gain, which may cause spectral broadening - if this occurs, a modal velocity should be measured.

Table 1 lists situations where the ratio of E/e’ should be interpreted with caution. Tissue e’ may be reduced in situations where the mitral annulus might be tethered by calcium or prosthetic rings.[26] Caution should be used when using E/e’ in LV disorders such as hypertrophic cardiomyopathy[27] and myocardial infarction,[28] as the downward movement during diastole can be influenced by upward movement during systole.[29)30] Conversely, the transmitral E measurement may be the source of misleading information in the setting of moderate to severe mitral regurgitation (MR)[31] and severe LV dysfunction.[25] In patients with constrictive pericarditis, LV diastolic properties are usually well preserved despite increased LV filling pressure,[32] and the positive correlation of e’ with LV filling pressure leads to an inverse relationship between E/e’ and LV filling pressure.[33]

Table 1. Situations where the use of E/e’ may be unreliable

Tachycardia with fusion of E and A velocities
Unreliable measurement of E velocity
- Significant mitral regurgitation (>2+)
Unreliable measurement of e’ velocity
- Mitral valve repair or replacement
- Severe mitral annular calcification
- Significant mitral stenosis
- Presence of left bundle branch block
Significant aortic regurgitation (>2+)

Alternative Approaches

The E/e’ ratio is an imperfect marker that should be supplanted or supplemented by other echocardiographic and even invasive measurements under certain circumstances. Other echocardiographic methods include measurement of pulmonary venous waveforms, duration of Ar velocity and the time difference between Ar and A-wave duration (Ar-A; with increased LV filling pressure, Ar velocity and duration increase).[20] Flow propagation velocity of mitral inflow (Vp) is evaluated as the slope of the first aliasing velocity during early ventricular filling. It is measured from the mitral valve plane to 4 cm distally into the LV cavity and > 50 cm/s is considered normal.[34] Vp can be used to predict LV filling pressure by combination with E velocity (E/Vp)[34] or IVRT {LV end-diastolic pressure = 4.5 × {10^3/(2 × IVRT + Vp) - 9]}.[35] In patients with depressed LVEF, a E/Vp ratio > 2.5 predicts LV end-diastolic pressure >15 mm Hg,[36] and an E/Vp ratio > 1.5 can be used as a prognostic marker in the prediction of in-hospital heart failure and survival after an acute myocardial infarction.[37] However, this parameter can be influenced by many factors including elastic recoil of the LA and LV, the diastolic properties of the LV, and LA pressure, so patients with normal LV systolic function (normal LV volumes and EF) and elevated LV filling pressures can have normal Vp.

Recently, global and regional diastolic function has been analyzed using strain and strain rate derived from speckle tracking and velocity vector imaging. These techniques do not have the limitation of angle dependency and have been validated with sonomicrometry,[38] and applied clinically.[39] Global diastolic strain rate during IVR (SR_{IVR}) by 2-dimensional speckle tracking imaging is a preload independent parameter. E/SR_{IVR} can predict LV filling pressure in patients with normal LVEF and regional dysfunction.[40] Because diastolic untwisting of the LV represents elastic recoil, a reduced rate of untwisting indicates the presence of diastolic dysfunction.[41] Decreased left atrial longitudinal strain during systole (< 30%) is associated with increased LV filling pressure.[42] However, the evidence base for using deformation imaging techniques in the evaluation of diastolic dysfunction requires further study.

In conclusion, the ratio between transmitral inflow and tissue velocity is a robust marker in the prediction of LV filling pressure. However, it is imperfect and should be interpreted with consideration of many situations that can affect this value. For this reason, this parameter should be supplemented by other echocardiographic and even invasive measurements under certain circumstances.

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