Time-varying effective mitral valve area: prediction and validation using cardiac MRI and Doppler echocardiography in normal subjects

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Bowman, Andrew W., Paul A. Frihauf, and Sándor J. Kovács. Time-varying effective mitral valve area: prediction and validation using cardiac MRI and Doppler echocardiography in normal subjects. Am J Physiol Heart Circ Physiol 287: H1650–H1657, 2004. First published January 29, 2004; 10.1152/ajpheart.00269.2004.—Precise knowledge of the volume and rate of early rapid left ventricular (LV) filling elucidates kinematic aspects of diastolic physiology. The Doppler E wave velocity-time integral (VTI) is conventionally used as the estimate of early, rapid-filling volume; however, this implicitly requires the assumption of a constant effective mitral valve area (EMVA). We sought to evaluate whether the EMVA is truly constant throughout early, rapid filling in 10 normal subjects using cardiac magnetic resonance imaging (MRI) and contemporaneous Doppler echocardiography, which were synchronized via ECG. LV volume measurements as a function of time were obtained via MRI, and transmitral flow values were measured via Doppler echocardiography. The synchronized data were used to predict EMVA as a function of time during early diastole. Validation involved EMVA determination using Eq. 1 the short-axis echocardiographic images near the mitral valve leaflet tips, 2) the distance between leaflet tips in the echocardiographic parasternal long-axis view, and 3) the distance between leaflet tips from the MRI LV outflow tract view. Predicted EMVA values varied substantially during early rapid filling, and observed EMVA values agreed well with predictions. We conclude that the EMVA is not constant, and its variation causes LV volume to increase faster than is reflected by the VTI. These results reveal the mechanism of early rapid volumetric increase and directly affect the significance and physiological interpretation of the VTI of the Doppler E wave. Application to subjects in selected pathophysiological subsets is in progress.

diastolic function; magnetic resonance imaging; E wave; transmitral flow

QUANTITATIVE, NONINVASIVE left ventricular (LV) diastolic function assessment often relies on determination of transmitral flow velocity and LV chamber volume. For example, invasive determination of LV chamber stiffness (which can be illustrated as the slope of a pressure-volume curve) requires simultaneous measurement of LV pressure and volume (16, 17). The availability of high-fidelity pressure transducers allows us to make precise pressure measurements, but precise volume measurements [even with a conductance catheter (29)] present a continuing challenge. One common approach to measure LV volume change involves transmitral flow measurement with Doppler echocardiography (16, 18) and computation of the velocity-time integral (VTI) of the Doppler flow profile (in units of cm) multiplied by the effective mitral valve area (EMVA, in units of cm²) to compute the diastolic stroke volume (in units of cm³) entering the left ventricle. More specifically, the volume that enters the left ventricle during filling must be equal to the integrated velocity of flow across the mitral valve times the effective area of the valve, or

\[ \text{LV}(t) - \text{LV}_m = \text{EMVA} \int E(t) \, dt \] (1)

where \( \text{LV}(t) \) refers to the LV volume as a function of time, \( \text{LV}_m \) is the LV volume before the mitral valve opens, EMVA is the (constant) effective mitral valve area, and \( E(t) \) is the echocardiographic Doppler E wave velocity as a function of time. However, to determine LV volume as a function of time during the filling process, this approach is accurate if and only if the EMVA remains constant throughout filling (15, 16).

We previously evaluated left heart function in healthy, young adult volunteers in a study that combined Doppler echocardiographic flow data with cardiac magnetic resonance imaging (MRI) volume data, which were synchronized via ECG (4). This study noted that contrary to what is expected from Eq. 1, by the time the peak velocity of transmitral early rapid filling (Doppler E-wave maximum) is attained, the majority of the MRI-determined, early filling volume has already entered the left ventricle (Fig. 1)! Consequently, the maximum rate of volume increase identified via MRI precedes the peak of the E wave obtained via echocardiography, which is also in apparent conflict with Eq. 1. The discord between these observations and Eq. 1 may be resolved if the EMVA is permitted to vary as a function of time. Indeed, the apparent discrepancy between Eq. 1 and the findings in Fig. 1 motivates the present study. Accordingly, we evaluated EMVA as a function of time during diastolic early rapid filling in young, healthy adults using a combined MRI-echocardiographic approach. We sought improved characterization of the time dependence of EMVA during diastole to gain additional insight into the physiology of LV diastolic function and into the interpretation of the commonly used methods of measuring LV volume change during early rapid filling.

METHODS

Cardiac MRI. After we obtained appropriate informed consent according to Washington University Medical Center Human Studies Committee guidelines, we performed a complete functional cardiac MRI study and concurrent two-dimensional Doppler echocardiography on 10 normal subjects (5 men and 5 women). The MRI portion of our study was previously described (3, 4). Briefly, for the MRI study, the subjects were scanned with a 1.5-T Philips Gyroscan MRI system...
repetition time, echo time, and cardiac phases triggered from the ECG R wave, which covered the 10-s breathholds per slice, and each cine loop was divided into 20 phases triggered from the ECG R wave.

The initial four-chamber view was used to plan a short-axis cine-stack protocol of between 18 and 20 slices (9 mm thick with zero gap) that spanned from the apex of the ventricles through the superior-lateral decubitus position by an experienced sonographer who was certified by the American Society of Echocardiography. An Acuson Sequoia (Acuson; Mountain View, CA) echocardiographic imaging system was used that was equipped with a 3.5-MHz transducer. The simultaneous limb lead II of the ECG was recorded and displayed on the image. The sample volume for transmitral Doppler imaging was placed at the mitral leaflet tips in the apical four-chamber view in accordance with American Society of Echocardiography criteria (22).

To minimize artifacts (to the extent possible) due to misalignment between the imaging beam and the flow, E wave data were obtained by aligning the scan direction along the line of motion of transmitral flow. Additionally, echocardiographic cine loops of the parasternal long axis (PSL), short axis at the level of the mitral valve leaflet tips, and M-mode views of the mitral valve were obtained in each subject in accordance with American Society of Echocardiography protocols (28). All echocardiographic data were stored digitally on magnetooptical disk for subsequent off-line analysis using ViewPro (Freeland; Westfield, IN) and Paint Shop Pro software. Baseline filters were set to their lowest settings.

As previously reported (4), once the chamber volumes were determined from the MRI images, chamber volume data (from MRI) and flow (from echocardiography) were synchronized using the ECG QRS complex as a fiducial marker (as shown in Fig. 1). Care was taken to pick representative images of the transmitral flow profile at heart rates as similar as possible to those obtained during the MRI scan.

**EMVA prediction.** If the EMVA is permitted to vary as a function of time, Eq. 1 can be rewritten more precisely as

$$\int_{V_0}^{V_f} \frac{dV}{d\tau} \, d\tau = \int \left[ \int \left( \frac{dV}{d\tau} \right) \, d\tau \right] \, d\tau$$

where $V_0$ is the initial volume at the beginning of the diastolic filling phase and $V_f$ is the final volume at the end of the diastolic filling phase.

In this study, the $d[LV(t)]/dt$ term is derived from the MRI volumetric data, and the $E(t)$ term is calculated from the echocardiographic transmitral flow data.

To differentiate the LV volume curve obtained via MRI, a third-order spline was fit through the LV volume data points that occurred during the Doppler E wave using MatLab 5.3 (MathWorks; Natick, MA). The derivative of the LV volume spline fit was numerically calculated, and the values of the derivative at the same discrete points were interpolated to obtain the LV volume derivative curve.

Doppler echocardiography. Either immediately before or after the cardiac MRI exam and while subjects were still in the MRI laboratory, clinical echocardiographic images were obtained all subjects in the left lateral decubitus position by an experienced sonographer who was certified by the American Society of Echocardiography. An Acuson Sequoia (Acuson; Mountain View, CA) echocardiographic imaging system was used that was equipped with a 3.5-MHz transducer. The simultaneous limb lead II of the ECG was recorded and displayed on the image. The sample volume for transmitral Doppler imaging was placed at the mitral leaflet tips in the apical four-chamber view in accordance with American Society of Echocardiography criteria (22).

To minimize artifacts (to the extent possible) due to misalignment between the imaging beam and the flow, E wave data were obtained by aligning the scan direction along the line of motion of transmitral flow. Additionally, echocardiographic cine loops of the parasternal long axis (PSL), short axis at the level of the mitral valve leaflet tips, and M-mode views of the mitral valve were obtained in each subject per standard protocols (28). All echocardiographic data were stored digitally on magnetooptical disk for subsequent off-line analysis using ViewPro (Freeland; Westfield, IN) and Paint Shop Pro software. Baseline filters were set to their lowest settings.

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as the MRI LV volume points were used to calculate the EMVA in Eq. 3.

In each subject, three transmirtal Doppler E waves were selected and fit using model-based image processing, a previously validated technique (9, 14) written in LabView 6 (National Instruments; Austin, TX), to yield a numerical representation of the continuous contour of each E wave (Fig. 3). These fits were averaged for each subject (10), and the average fit was used to determine the value of \( E(t) \) at the desired time points used in Eq. 3.

**EMVA measurement.** To validate the prediction of time-varying EMVA made by Eq. 3, the EMVA was measured throughout early rapid filling via three methods. First, using the echocardiographic short-axis cine loop obtained at the level of the mitral leaflet tips, the cross-sectional area of the mitral valve was traced during diastole (Fig. 4A). Second, using the echocardiographic PSL cine loop, the distance between the mitral leaflet tips was measured during diastole (Fig. 4B). This distance can be used to approximate the diameter of the mitral orifice at its effective opening (i.e., at the leaflet tips). Assuming a circular mitral orifice during flow for the sake of simplicity, the diameter of the orifice can be used to estimate the EMVA. The distance between the leaflet tips and not the diameter of the mitral orifice at the level of the annulus was measured, because the Doppler E waves were obtained at the level of the mitral valve leaflet tips and not at the level of the annulus. Third, using the MRI LVOT view (analogous to the echocardiographic PSL view), the time-varying distance between the mitral leaflet tips can also be measured during diastole (Fig. 4C). Similar to the PSL measurement, this distance approximates a mitral valve diameter and can be used to estimate the EMVA. Intraobserver variability was determined using five randomly selected images from each view used to measure EMVA.

**RESULTS**

**Average EMVA.** Before calculating the EMVA as a function of time, we determined its average value during early rapid filling. The average EMVA was calculated in each subject by dividing the MRI-determined volume by which the left ventricle filled during early rapid filling by the VTI of the entire Doppler E wave. For all subjects, the overall average EMVA during early rapid filling was \( 5.5 \pm 2.0 \text{ cm}^2 \) (mean \( \pm \text{SD} \)). We then calculated what the LV volume curve would look like if the EMVA were constant at its average value throughout the Doppler E wave. In 9 of the 10 subjects, the LV volume curve that was calculated assuming a constant EMVA systematically underestimated the actual MRI-determined LV volume at each time point (Fig. 5).
EMVA as a function of time. Using Eq. 3 in conjunction with the MRI LV volume curve and the echocardiographic Doppler E wave, the time-varying EMVA was predicted. As indicated in Fig. 6A, the predicted EMVA varied considerably, peaked early during transmitral flow, and progressively diminished as the duration of flow continued (compare Fig. 6, A and B).

To validate whether the EMVA truly behaves as predicted by Eq. 3, we calculated the mitral valve area using measurements made from the echocardiographic short-axis cine loop at the mitral leaflet tip level, the echocardiographic PSL cine loop, and the MRI LVOT cine loop. As also demonstrated in Fig. 6A (see also Animations 1–3, at http://ajpheart.physiology.org/cgi/content/full/00269.2004/DC1), the EMVA values as a function of time that were calculated from the three methods show strong agreement with the predicted values for EMVA as determined via Eq. 3. Intraobserver variability for EMVA measurement was 4.9%.

Interestingly, the EMVA derived from Eq. 3 predicts in all subjects that the maximum EMVA is obtained before the peak of the Doppler E wave. To evaluate this phenomenon more carefully and to remove the potential of systematic error due to differences between imaging modalities, we examined the same events using a single imaging modality. Accordingly, transmitral E waves and Doppler M-mode images of the mitral valve were synchronized relative to the R wave. In 9 of 10 subjects, relative to the R wave, the peak displacement of the anterior mitral leaflet occurred before the peak velocity of the E wave (Fig. 7). On average, the E wave reached its peak 20 ± 16 ms after the maximum displacement of the anterior mitral valve leaflet.

**DISCUSSION**

Classic physiology papers and textbooks state that the average size of a normal mitral valve is 4–6 cm² (7, 8, 30). Although the motion of the mitral leaflets throughout diastole has been chronicled (25, 26), and changes in the mitral annulus area during the cardiac cycle have been reported (20), the derivation of the EMVA time dependence and its impact on diastolic function determination has not been previously considered. On initial examination, it may appear that some of the predicted values for the EMVA during early filling (>10 cm²) are too large to be physiologically or functionally attainable. To more fully evaluate the physiological possibility of such EMVAs, in two of the subjects, a concomitant mitral valve area measurement was also performed via the pressure half-time method (11–13) and yielded an average of 4.9%.

Fig. 5. LV volume curve (MRI measured) for a normal subject during diastole (●) superimposed with a predicted LV volume curve (gray line) using the velocity-time integral of the E wave and assuming a constant EMVA. Note how the predicted LV volume curve systematically underestimates the actual LV volume at every data point. Values on the time axis refer to the time (in ms) from the peak of the ECG QRS complex.

Fig. 6. Alternative imaging views of measured EMVA vs. predicted EMVA as a function of time (A) temporally linked with a transmitral flow image for one subject (B). Measured EMVA from the basal short-axis echocardiographic images near the mitral valve (●), EMVA calculated from the distance between the mitral leaflet tips from the echocardiographic parasternal long-axis view (○), and EMVA calculated from the distance between the mitral leaflet tips from the MRI LV outflow tract view (■) are shown. Predicted EMVA (based on Eq. 3) is also indicated (■, dashed line). Note the similarity of predicted and measured shapes, which consist of an early, phasic, rapid increase and subsequent decrease in EMVA. Peak of the ECG QRS complex (gray vertical line) and beginning and end of the Doppler E wave (two black vertical lines) are also shown.
is well established that the peak transmitral pressure gradient precedes peak flow (6), and the pressure gradient is the driving force for opening the valve and initiating flow. Additionally, earlier studies in dogs documented that the valve leaflets begin to open even before LV pressure decreases below left atrial pressure (26). As previously documented (5), a vena contracta effect may also exist, which would draw the leaflet tips together slightly after maximum valve opening. When the velocity of blood between the leaflets increases, the pressure between the leaflets that results from this effect decreases (via the Bernoulli equation), and this pressure decrease may contribute to the initial decrease in EMVA that is seen at the time of the peak E-wave velocity. Another factor is that the Doppler method can only image flow along the line of sight of the echo beam. It is possible that flow with a slight transverse component, which is undetected by the Doppler method, may aid in leaflet separation during the earliest portions of diastolic filling.

In previous studies modeling mitral valve mechanics, researchers postulated that at a certain transmitral threshold velocity, the valve attains its maximum effective cross-sectional area and remains at that area until transmitral flow decreases below this threshold velocity (1). Our results illustrate that the EMVA changes throughout early rapid filling. However, due to the short time intervals involved in the duration of the E wave coupled with the finite (30–50 ms) temporal resolution of the MRI method, it may be difficult to precisely determine any transmitral threshold velocity for maximum valve opening that may exist using our methods.

The existence of a time-varying EMVA is physiologically attractive and potentially significant because of its functional implications. In terms of the physiology of diastolic function and LV filling, our results provide insight into the design of the human heart. In functional terms, it is desirable for the left ventricle to fill as rapidly as possible. One way to facilitate such rapid filling would be to allow the largest opening for the passage of blood (the EMVA) to occur essentially at the same time as the development of the maximum atrioventricular pressure gradient. Once the peak of the E wave is reached, the transmitral pressure gradient driving the forward flow has diminished to zero (6); thus the driving force for LV filling has ended. The remainder of the E wave, i.e., the deceleration portion, is generated by a reversal of the atrioventricular pressure gradient and reflects a combination of inertial and chamber stiffness effects (16).

Additionally, a commonly used clinical index for diastolic function is the Doppler E wave deceleration time (DT). Our results suggest that the volume of blood that enters the left ventricle during the E wave DT is less than half of the total E wave filling volume, although the deceleration portion of the E wave usually accounts for more than half of the total E wave duration (in healthy subjects). This, in conjunction with the reversal of the transmitral pressure gradient at the peak of the E wave, underscores that LV filling during the E wave DT is dominated by inertial forces and has less impact on the total E wave filling volume than might be indicated by the E wave VTI, assuming a constant EMVA. Studies to evaluate the significance of these findings

Fig. 7. ECG synchronized (gray vertical line) transmitral Doppler E wave (A) with Doppler M-mode (B) of the mitral valve leaflets for a representative subject. Note that the maximum displacement of the anterior leaflet (dashed black vertical line) occurs before the peak of the E wave (solid black vertical line).

Fig. 8. MRI short-axis velocity phase-encoded image of transmitral flow during early diastole in one of the subjects in this study. Note that the area of the flow jet in a plane at the leaflet tips is measured to be 12.1 cm² in this example. MV, mitral valve; TV, tricuspid valve.
in the setting of abnormal transmitral filling patterns are presently in progress.

Limitations. Because the MRI scan and echocardiographic study were contemporaneous but not simultaneous, we were unable to assure the maintenance of an absolutely constant heart rate in our subjects. Because the MRI imaging involved frequent breathholds, the measured heart rate of some subjects was found to be different during the MRI scan than during the echocardiography study (from \( \sim 60 \) to 80 beats/min). However, during such minor changes in heart rate, the change in duration of systole is minimal, and the change in duration of diastolic early rapid filling is similarly minimal because the change in the cardiac cycle (R-R interval) duration is primarily accounted for by change in the duration of diastasis, the interval between the Doppler E and A waves when no significant transmitral flow occurs. Additionally, we note that the timing of events during systole and early diastole was consistent between the echocardiographic measurements and the MRI measurements even when the heart rates of subjects varied somewhat between the two studies. However, we also note that the use of breathholds during the MRI exam and its absence during the echocardiographic exam may introduce some differences in the transmitral pressure gradients present during the two studies. Because all of the subjects were young, were in good physical condition, and performed short (\( \sim 10 \) s) breathholds, such differences in pressure gradients were likely minimal.

As stated above, the temporal resolution of the MRI scans ranged from \( \sim 30 \)–\( 50 \) ms, which corresponds to a frame rate of 20–33 frames/s. Although faster frame rates are achievable using other MRI protocols, this rate was selected to balance the simultaneous needs of subject comfort, breathhold duration, scan duration, and spatial resolution. Accordingly, the average temporal resolution of the MRI scans (39 ms) closely mirrors the temporal resolution of the echocardiographic cine loops (33 ms). Furthermore, the data presented in Figs. 5 and 6A clearly show that multiple data points during early rapid filling were obtained via all methods, which consistently demonstrates how the EVMA varies throughout early rapid filling.

Because the MRI volumetric data were acquired using 9-mm-thick slices, there is the possibility of systematic error in the volumes reported in this study. However, the technique employed in this study is the present MRI research standard. Manual tracings of the chambers may also raise concern, but it has also been the standard approach for chamber volume determination. A recently developed automated edge detection method for volume measurement showed excellent agreement relative to the present gold standard, which consists of manually traced segmental volumes (27).

To calculate the derivative of the LV volume curve during early rapid filling, the LV volume data points were fit with a third-order spline to render the LV data more continuous. Limitations of curve fitting in this manner are obvious and could lead to some inappropriately large derivatives. To minimize these errors, care was taken to select data points for use in Eq. 3 that were not too close in time to the onset of the Doppler E wave (which, in conjunction with errors arising from calculating MRI volumes using 9-mm-thick slices as well as limitations in the temporal resolution of MRI data in the setting of averaged, continuous E wave data, may yield a predicted EMVA larger than the cross-sectional LV area). However, in some cases, the initial data point for the predicted EMVA was still exorbitantly large. We note that even in these cases, subsequent predicted EMVA data points closely mirrored the calculated EMVA values.

We also note that the data indicate that the MRI-determined LV volume begins to increase before the beginning of the Doppler E wave (see Fig. 1). The shape of the LV volume curve is similar in all subjects in this study and is consistent with other published MRI-derived volume curves (4, 27), all of which indicate a single data point of minimum LV volume even in scans with sufficient temporal resolution to image multiple time points during isovolumic relaxation. This slight rise in volume before mitral valve opening and the onset of the E wave is likely an artifact of the MRI-volume measurement method. The rotational/torsional and slight geometric changes in the shape of the left ventricle during isovolumic relaxation may lead to the appearance of mildly increasing volume in the imaging plane employed in this study. The slice thickness of 9 mm may also mask small longitudinal motions of the mitral valve that serve to conserve LV volume during diastolic isovolumic wall relaxation. Consistently, however, the data show that at the onset of the Doppler E wave, the rate of LV filling (measured via MRI) increases dramatically, which thereby reinforces our confidence in the accuracy of the temporally aligned datasets (4).

We note that the calculated EMVAs via the echocardiographic PSL and MRI LVOT methods agreed with one another better than the EMVA calculated via the echocardiographic short-axis method. This is not surprising, because the PSL and LVOT views are essentially identical. The similar results obtained from these views further underscore the reliability of using both echocardiographic and MRI data to quantify cardiac events. However, the echocardiographic short-axis-view data may have diverged from the other data, because the imaging plane may not have been precisely at the level of the mitral leaflet tips. Furthermore, the mitral valve annulus (to which the leaflets are attached) exhibits longitudinal motion during diastole as the mitral valve plane moves away from the apex during LV filling (which generates the Doppler tissue imaging-based E’ wave). This motion may further exacerbate any misalignment of the imaging plane. Because the echocardiographic PSL and MRI LVOT are both long-axis views, the tips of the mitral leaflets can be visualized at all times, which eliminates the misalignment and through-plane motion issues inherent in short-axis views.

A full MRI mitral valve flow study protocol using velocity phase encoding was not performed on all of the subjects. Our goal was to precisely determine EMVA as a function of time, and although the phase-encoded velocity images can illustrate how large the cross-sectional area of the jet of mitral flow may be (see Fig. 8), it is difficult or impossible to measure anatomical features (such as mitral valve leaflet tips) with the precision that we required using this method. Similarly, EMVA was not calculated using the Doppler M-mode of the mitral valve, because in most images, the posterior leaflet was insufficiently well seen to make reliable measurements. Additionally, there was the short-axis misalignment concern as previously discussed. Nonetheless, due to the superior temporal and spatial resolution of M-
mode Doppler, it was used to compare the timing of maximal anterior leaflet displacement with the peak Doppler E wave velocity. It may appear possible that the measured difference in time between the peak displacement of the anterior mitral leaflet and the peak of the E wave (see Fig. 7) is an artifact of different processing times between the two imaging modalities of the echocardiography machine. However, we note that the onset of the E wave (via the transmural view) is virtually simultaneous with the opening of the valve (via M-mode) in all subjects (data not shown), which reinforces our confidence that the measurement reflects real physiology and is not a result of a systematic error due to either imaging modality or hardware-related image-processing times.

It was not the intention of this study to evaluate flow across the mitral valve in the sense of fluid dynamics, because such studies have been previously reported (2, 5, 19, 21, 24). It was our intention to predict and measure, using standard clinical imaging modalities, the size of the EMVA during early rapid filling. We also want to underscore that the majority of the early rapid filling volume enters the left ventricle during the initial component (about the first 80–100 ms) of early rapid filling. This is made possible by the generation of the largest EMVA during this interval of transmural flow.

We conclude that during early rapid LV filling, the EMVA is not constant but rather is time dependent and often reaches areas larger than those previously reported in anatomical or pathological studies. The valve area is largest early during transmural flow and decreases as flow diminishes. This facilitates rapid filling of the left ventricle in the shortest amount of time and leads to >50% of the E wave volume entering the left ventricle by the peak of the E wave. Data also indicate that the maximum EMVA occurs before the peak of the E wave, which likely mirrors the magnitude of the transmural pressure gradient. These results highlight the limitations in calculating LV filling volume as a function of time using only the VTI of the Doppler E wave and an assumed constant EMVA. Application of these methods to hearts with abnormal transmural filling patterns is in progress.

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