Validation of Established Standard Values for the Correlation of E/e' Ratio and Left Ventricular Diastolic Pressure in a Study of 190 Patients with Dyspnea – What are the Main Factors for the Observed Discrepancies?

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Abstract

Aim: In the past, Mitral E/e' ratio has been recommended for detecting elevated left ventricular filling pressures. However, more recently, gender specific differences in E/e' ratios have been demonstrated. The aim of this prospective study was to validate the established standard values for the correlation of E/e' ratio and left ventricular end diastolic pressure (LVEDP) in 190 consecutive patients with dyspnea in terms of age and gender differences.

Methods and results: 190 patients had sufficient echogenicity to allow complete assessment of the Doppler and tissue Doppler parameters. Overall, there was only a weak significant correlation between E/e' ratio and LVEDP pre laevo cardiography (R=0.24, P=0.006). In patients with ejection fraction (EF) > 50% there was no significant correlation. Female patients had higher baseline E/e' ratios than male patients. An E/e' ratio > 15 for predicting an elevated LVEDP was only significant in male but not in female patients. E/e' ratio increases progressively with age and is remarkable higher in women than in men. Irrespective of gender, a stratification of E/e' ratio < 8, 8-15 and > 15 did not allow prediction of LVEDP.

Conclusions: Only male patients showed a significant correlation (R = 0.29, P = 0.012) between their E/e' and LVEDP with respect to difference in gender. Excessively high E/e' ratios measured in women were less pathognomonic for diastolic dysfunction than in men.

Keywords: LV diastolic pressures; Mitral E/E' ratio; Gender differences; Cardiac catheterization; EF

Introduction

Echocardiographic imaging, especially pulsed-wave Doppler for the analysis of left ventricular diastolic filling, developed as standard technique for evaluating dysfunction and allows prognosis and therapy. More recently, in the hope of finding a new echocardiographic parameter to improve noninvasive measurement, there have been several studies which are focused on the usefulness of Tissue Doppler imaging (TDI). In particular, for measuring the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e'), also known as the E/e' ratio. One study demonstrates that there is a correlation with left ventricular diastolic pressure (LVDP), especially with E/e' >15 [1-3], the other studies have shown that in patients without heart failure E/e' ratio has a greater correlation with the pre-a wave left ventricular diastolic pressures (pre-a LVDP) than with LVEDP [4,5]. Other observational research reveals a relation between E/E' ratio and the pulmonary capillary wedge pressure (PCWP) [6,7]. Moreover, E/E' ratio has been shown to be correlated with brain natriuretic peptide (BNP) [7-9].

Thus, the current ESC Guidelines from 2012 for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommend trans thoracic echocardiography for the evaluation of diastolic function using TDI and assessment of the E/e' ratio. It is stated that the E/e' ratio correlates with LVEDP and an E/e' ratio >15 is indicative of diastolic dysfunction. Furthermore, it is stated that parameters of diastolic dysfunction depend on age, heart rate and body size [10].

Over the course of 2 years (October 2010- November 2012), 190 consecutive patients of different age who were referred for echocardiographic examination and cardiac catheterization were examined.

The aim of this study was to validate the established standard values with respect to the correlation of E/e' ratio and left ventricular filling pressure on the basis of 190 patients with dyspnea undergoing cardiac catheterization. Furthermore, the effect of gender and age on echocardiographic parameters was analyzed.

Methods

The study group consisted of 190 consecutive patients whose echocardiographic examination included both Doppler assessment of trans mitral flow velocities and tissue Doppler imaging of particularly the medial mitral valve annulus. All patients were referred due to clinically indicated left heart catheterization on the basis of dyspnea. There were 110 (57.9%) male and 80 (42.1%) female patients with an age of 69 ± 12 years. 144 (75.79%) patients were in sinus rhythm, while 46 (24.21%) patients had atrial fibrillation.

The patients had a mean age of 69 ± 12 years. The mean systolic pressure was 147 ± 28 mmHg and the mean diastolic pressure was 71 ± 15 mmHg. All of the patients gave their informed consent and the Ethical Committee of the University of Bonn checked the study protocol.

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Catheter measurements

All 190 patients underwent left heart catheterization using a 5 or 6F pigtail catheter which was inserted in the right femoral artery and placed retrogradely in the left ventricular chamber and calibrated. The LVEDP was measured at the beginning of the rapid rise of left ventricular pressure after the atrial wave. To determine patients’ cardiac pump function, we used 35-45 ml of contrast material for ventriculography with a flow of 8-15 ml/s and measured the left ventricular pressure ratios before and after volume loading (laevo cardiography). In order to account for respiratory variation, measurements were taken during end-expiratory apnoea before volume loading and immediately after loading. Mean values over 5 cardiac cycles were used for analysis. ALVEDP ≤ 12 mmHg was considered normal.

Echocardiographic measurements

Immediately before invasive measurements were taken, echocardiography was performed using the ultrasound system Vivid S6 (GE, Healthcare; Israel). Mitral valve inflow was recorded in the apical four-chamber view using pulsed-wave Doppler echocardiography with the Doppler beam aligned parallel to the direction of flow and the sample volume at the leaflet tips. The measurements were taken by two investigators, who were not included in this study. Both performed Doppler echocardiography for over 5 years. To assess inter- and intra-observer variability, measurements were repeated in a selection of 30 randomly chosen examinations by a second independent observer. These measurements were also repeated one and six months after the first measurement.

The following parameters were measured: peak velocity of early E- and late A-waves, the E/A ratio and the deceleration time (DT). TDI of the mitral annulus was obtained from the apical 4-chamber view by positioning a 1.5 mm sample volume at the septal and lateral corners of the mitral annulus to calculate Septal e’, Lateral e’ and the Ratio’s Septal E/e’ , Lateral E/e’ and the average E/e’ ratio. The measurements of this study focus especially on the Septal E/e’ ratio. All Doppler signals were recorded with a chart recorder set at 100 mm/s. The average of three end-expiratory cycles was performed.

Additionally, the following echo cardiac graphic parameters were measured: the left ventricular end diastolic (LVEDV) and the end systolic volume (LVESV) as well as the left atrial volume (LAV) using the area-length method. Left ventricular dilation was defined as a >75 mL/m² LVEDV. The ejection fraction (EF) was calculated by the Simpson method using 2-dimensional images and compared with cardiac estimations. Left ventricular (LV) systolic dysfunction was defined as EF<50%.

Statistical analyses

All statistical analyses were performed with the statistic program IBM SPSS Statistics 21. Bivariate correlations were calculated using the Pearson Test. All P-values were two-tailed. Statistical significance was inferred when p<0.05. Descriptive data was expressed as mean ± standard deviation (SD). The T-test was used to compare the echo-Doppler variables between different subgroups of patients.

Results

General characteristics

Table 1 shows the clinical characteristics of the study population. All patients were referred for evaluation of angina, 66 (34.73%) with identified CAD and patients had been diagnosed with 18 (9.47%) with acute coronary syndrome. 93 (48.95%) patients showed an EF<50% and 97 (51.05%) had an EF ≥ 50%.

Mitral inflow pattern and left ventricular filling pressure

The correlation between Doppler measurements and LVEDP is shown in Table 2. There is a very weak significant correlation between Septal E/e’ ratio and the LVEDP pre laevo cardiography (R=0.24, P=0.006). E-wave velocity was also statistically correlated with LVEDP (R=0.20, P=0.013), as evident in Table 2. A significant correlation was found between DT and LVEDP pre- and post-laevo in patients with a ≤ 50% EF, but not in those with normal LV function (Figure 1).

E/e’ Ratio in the estimation of LVEDP in normal and decreased ejection fraction

In patients with decreased ejection fraction, there is still a weak correlation between Septal E/e’ ratio and LVEDP pre-laevo (R=0.24, P=0.056). Furthermore is shown in Table 3, Septal E/e’ ratio was higher in the study population with decreased EF than in those with normal EF (Septal E/e’ ratio=15.55 ± 7.4).

Gender difference in the estimation of E/e’ ratio and LVEDP

Table 4 shows a significant correlation between Septal E/e’ ratio and the LVEDP pre laevo (R=0.29) in male patients. In fact, the statistical correlation of Septal E/e’ ratio was also shown in male patients with a ≤ 50% EF. However, an analogous correlation in female patients (Table 5) was not found. Similarly, the influence of EF was only notable in male and not in female patients (Table 5).

Table 1: Baseline characteristics n=190.
LVEDP post laevo

| Parameter | all EF<50% | all EF ≥ 50% |
|-----------|------------|--------------|
| E         | 0.132 (0.210) | 0.194 (0.219) |
| E/A       | -0.061 (0.426) | -0.118 (0.470) |
| DT        | -0.302 (0.003) | -0.354 (0.022) |
| Septal F  | -0.153 (0.156) | -0.199 (0.217) |
| Lateral r | -0.210 (4211)  | -0.325 (257)   |
| Septal E/E | 0.152 (0.163) | 0.193 (0.240) |
| Lateral E/E | 0.080 (0.311) | 0.272 (0.348) |

P-values are shown in parenthesis: LVEDP, EF and DT indicates left ventricular enddiastolic pressure, ejection fraction and deceleration time respectively.

Discussion

Despite of numerous studies, the question of whether E/e’ ratio can be used as a predictor for LVEDP still yields contradictory results.

According to the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012, high left ventricular filling pressure is associated with an elevated E/e’ ratio greater than 15 [10]. Furthermore, it states that an E/e’ <8 is a reliable predictor of normal LVDP cases with intermediate E/e’ 8-15, in the range referred to as the

E/e’ ratio Stratification and LVEDP: A stratification of E/e’ ratio < 8, 8-15 and > 15 did not allow prediction of LVEDP in the total patient population (Figure 2).

Table 6 demonstrates that an E/e’ ratio> 15 is correlated with an elevated LVEDP (R=0.39 and P= 0.059) in men. In women however, there is a significant negative correlation between E/e’ ratio <8 with LVEDP pre-laevo (R=-0.74, P=0.023).

E/e’ Ratio as function of age and sex: The E/e’ ratio increases proportionally with age in both male and female patients. However, the E/e’ ratio increases disproportionately with age in female patients as compared to male patients (Figure 3). As is demonstrated in Figure 4, the E/e’ ratio increases alongside LVEDP in the total patient population. Moreover, female patients have a higher increase in E/e’ ratio in relation to LVEDP than male patients.

Table 6: LVEDP ingroups defined by values of septal E/E’ ratio (E/E’<8, E/E’ 8-15, E/E’>15).
that an early study demonstrating a high correlation between E/E´ratio and pre-a LVDP is independent of gender difference: Only the male study group shows a significant correlation between E/e´ ratio and pre-a LVDP, since 32% of patients with suspected or ascertained coronary artery disease [15,16], especially as a result of regional ischaemia in localized sites. Since the septal annulus site moves parallel to the ultrasound beam heart [17], this methodology is preferred by some cardiologists.

In this study, the stratification of E/e´ ratios as suggested by ESC Guidelines did not predict LVEDP. This was irrespective of a high prevalence of E/e´ ratios in our study population (the mean value was 21.3 ± 5.1 in patients with E/e´ ratio>15). Furthermore, there was no significant correlation between E/e´ ratio and LVEDP in patients with normal EF [10]. In contrast, there was a positive correlation in patients with depressed EF. It is important to note that our study included a large number of patients with both depressed and normal ejection fraction, which may account for the differences from other studies. Other study groups have already noted that EF is not solely determined by systolic pump function. On the contrary, it is a complicated interplay between ventricular filling pressures, compliance and stiffness of the LV, and is also influenced by several intrinsic and extrinsic factors [11].

**Septal E/e´ ratio vs. Lateral E/e´ ratio**

Previous studies have shown a stronger correlation between the E/e´ ratio and LVDP when using e´ velocity of lateral annulus [12-14] than of septal mitral annulus. In particular, this was shown in patients with suspected or ascertained coronary artery disease [15,16], especially as a result of regional ischaemia in localized sites. Since the septal annulus site moves parallel to the ultrasound beam heart [17], this methodology is preferred by some cardiologists.

Another limitation of this study is that the mean value of E/e´ ratio was abnormally high. This finding may be related to our echocardiographic performance: All patients were measured while lying on the catheterization table immediately before invasive measurements that are not usually performed upon supine subjects. This explains why it was not possible to demonstrate ultrasound beam of the lateral annulus in most of the examinations. As a result, the e´ velocity was reduced in E/e´ ratios which resulted higher than the average values found in the Guideline value [10]. Moreover, performing echocardiographic and invasive measurements nearly simultaneously was also very strenuous for our study patients – another possible reason for higher E/e´ ratios.

**Gender and age difference in diastolic function:** More recently, multiple studies have shown that diastolic function as assessed by echo-Doppler and TDI is influenced by age, among other factors. However, age emerged as the strongest contributor toward reducing average E e and toward increasing average A e and E/e´ ratio values [15,20]. In addition to this, the E/e´ ratio was noticeably higher in the highest three age decades [20]. Finally, a relation was shown between E/e´ ratio and gender [21-23]. A study, published in 2013, showed that baseline E/e´ ratios in men were lower in men than in women [23]. Furthermore, the changes in E/e´ ratios during the ageing process were similar for both men and women. Moreover, a significant proportion of patients over
the age of 40 and almost 50% in patients over 70 years old had an E/e’ ratio greater than 8.

The results of this are particularly interesting in the light of the above-mentioned findings, since we correlated Doppler parameters with invasive measurements. One of the most important findings of this study is that the Septal E/e’ ratio was only predictive in male patients for an elevated LVEDP, whereas female patients lacked any significant correlation. This is in accordance with higher baseline E/e’ ratios in female patients than in male patients [21-23]. A potential explanation for the latter finding is that the E/e’ ratio increases in female patients with increasing age disproportionately compared in male patients [12,23]. On the other hand, an E/e’ < 8predictive of a normal LVEDP in female patients was found, indicating that a normal E/e’ ratio measurement reveals normal diastolic function. One must consider that our study population is not a sample group. Nevertheless, the study population was well-balanced in terms of gender and cardiac events. Therefore, it is possible to claim that the excessively high E/e’ ratios measured in women are less pathognomonic for diastolic dysfunction than in men. Thus, it is important to adjust the established standard values for gender-specific and age-specific differences (Figure 5).

Several studies found a gender difference in terms of molecular patho physiological heart tissue [24-26]. A possible approach for this seems to be estrogen, which reduces CAD and hypertrophy of the myocardium by modifying the rennin angiotensin system (RAS) and declines after menopause [27]. Due to different tissue structures, women seem to generate different echocardiographic standard values than men [28].

Study limitation

The investigation of a sample group of patients undergoing cardiac catheterization was attempted. The selection of patients undergoing catheterization notes a contradiction referring to higher prevalence of cardiac disease. Nevertheless, all patients were clinically stable, during both echocardiographic and hemodynamic measurements, and no variety in blood pressure and heart rate were recorded.

To assure comparable echocardiographic and hemodynamic parameters, all patients were examined after 5 minutes of rest. Nevertheless, individual patient characteristics (i.e. obesity, poor acoustic windows or obstructive airway disease) may have influenced data acquisition. Particular care was taken to obtain Doppler parameters immediately before invasive parameters.

Conclusion

In clinical practice, gender differences play a decisive role in terms of assessing echocardiographic measurements. Our measurements showed that an E/e’ ratio > 15 can be a predictor for an elevated LVEDP in male patients, whereas an E/e’ < 8 predicted normal LVEDP in female patients. The findings of this study indicate that the effect of gender and age on diastolic function have to be considered when using E/e’ ratios to predict LVEDP. Larger studies should be processed to build a database of standard values that incorporate the gender- and age-specific differences that we found in this study.

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