

Role of tissue Doppler imaging in assessing left ventricular diastolic dysfunction severity

Does it hold the same ability?

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ABSTRACT

الأهداف: التحقق من القدرة التشخيصية لتصوير النسيج القلبي بالموجات فوق الصوتية عالية التردد (دوبلر) وذلك من أجل تحديد درجة اعتلال ضغط القلب الانبساطي.

الطريقة: أجريت هذه الدراسة التشخيصية السريرية في قسم القلب، مجمع السلمانية الطبي، المنامة، البحرين، واستمرت خلال الفترة من مايو إلى يوليو 2010م. شملت الدراسة في البداية 70 مريض ممن يعانون من ارتفاع ضغط الدم وعسر في التنفس. ومن ثم تم استثناء بعض المرضى حيث بقي 48 مريض ممن أتموا شروط الدراسة. تضمن البحث دراسة مفصلة للوظيفة الانبساطية بواسطة الموجات فوق الصوتية بالتوافق مع تحليل مستوى هرمون إفراز الصوديوم في البول (NT-proBNP).

النتائج: لقد تم تصنيف المرضى بناء على حدة القصور القلبي إلى 4 طبقات وذلك اعتماداً على معيار جمعية نيويورك لأمراض القلب. لقد بلغ عدد الذكور 28 ذكر (58%)، و20 أنثى (42%). حافظ التصوير النسيجي القلبي على علاقة طردية وطيدة مع معيار جمعية نيويورك لأمراض القلب، ونسبة هرمون إفراز الصوديوم في البول. لقد بلغ عامل الارتباط 0.8 ($p < 0.0001$). ويمكن حساب هرمون إفراز الصوديوم في البول عن طريق المعادلة المستنبطة من الارتباط التالي: $NT-proBNP = 93.8 \times (E/E') - 940$.

خاتمة: أثبتت هذه الدراسة مدى قدرة التصوير النسيجي القلبي على تعبير حدة اعتلال ضغط القلب الانبساطي، بالإضافة إلى دقة مثل هذا التصوير في التشخيص السريري. وتتطلب براعة تطبيق مثل هذا التصوير في استيعاب نقاط قصوره.

Objectives: To validate the diagnostic capability of tissue Doppler imaging in assorting the extent of diastolic dysfunction.

Methods: In this primary clinical research diagnostic study, we enrolled 70 patients with systemic hypertension presenting with shortness of breath

between May 2010 to July 2010 to Salmaniya Medical Complex, Manama, Bahrain. Forty-eight patients satisfied the inclusion criteria. They underwent extensive echocardiographic assessment of their diastolic function with simultaneous NT pro-B-type natriuretic (BNP) assay. The latter being the reference marker of diastolic defragment.

Results: Patients were classified according to the severity of heart failure into 4 classes of New York Heart Association (NYHA) Classification. Twenty-eight (58%) were males and 20 (42%) were females. The tissue Doppler imaging (TDI) maintained a steady positive correlation with both NYHA functional class and the PRO-BNP titre. Correlation coefficient was 0.8 with a $p < 0.0001$. N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be calculated from simplified formula derived from the correlation-pro-B-NP = $93.8 \times (E/E') - 940$.

Conclusion: The TDI can estimate the severity of diastolic dysfunction with striking certainty and tremendous clinical utility. Its limitation, however, has to be well addressed.

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Diastolic heart failure is defined as signs and symptoms of congestive heart failure, preserved left ventricle systolic function, and demonstrated elevated filling pressure, invasively or non-invasively, in the absence of alternate diagnosis.¹ Further, the echocardiographic criteria estimating the diastolic properties of the left ventricle are continuously evolving and actively validated. The conventional pulse wave parameters of the left ventricle inflow demonstrated to be highly influenced by the various hemodynamic loads and the intravascular volume. Recently, the myocardium tissue Doppler indices have over-ridden the conventional pulse wave Doppler method, in terms of accuracy and reproducibility, for estimating left ventricle-filling pressure. The consensus impression concerning its utility in left ventricle pressure assessment has been debated lately. The N-terminal pro B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) were strongly correlated with diastolic dysfunction severity. Being a sub-analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) preserved trial, the echocardiographic indices did not include the tissue Doppler imaging.^{2,3} The aim of our study is to ascertain the correlation between tissue Doppler imaging (TDI) derived velocity and plasma levels of NT-proBNP in patients with systemic hypertension. This will help to redefine its clinical potentiality in assessing the degree of diastolic derangement.

Methods. In this primary clinical research diagnostic study, we enrolled 70 patients with systemic hypertension presenting with shortness of breath between May 2010 to July 2010 to Salmaniya Medical Complex, Manama, Bahrain. Forty-eight patients satisfied the inclusion criteria. Patients satisfied the definition of congestive heart failure as adopted by the Framingham Criteria.⁴ Furthermore, we demonstrated elevated filling pressures with preserved systolic function (ejection fraction (EF) >50%) categorizes into diastolic heart failure subgroup.

The inclusion criteria were: age >18 years, systemic hypertension, and in sinus rhythm. Exclusion criteria were: acute coronary syndrome, impaired systolic function (EF <50%), significant valvular lesions, regional wall motion abnormalities, pericardial effusion or constriction, previous cardiac surgery, or patient with renal impairment (estimated glomerular filtration rate <90 ml/min/1.73 m²).

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The ethical committee approval was obtained after submitting the proposal to the research committee of the institute. All patients were consented prior to enrollment. The enrollment and participation of the patients were entirely optional, and complies with Helsinki declaration.

Echocardiography. Comprehensive transthoracic echocardiography was performed by an experienced operator blinded to the result of the NT-pro BNP assay. The various parts of cardiac cycles were timed according to simultaneous ECG recording. The study was reported and finalized at the same setting and stored in archive system using the Excerella 1.2 (Philips, Zuid-Holland, Netherlands) workstation. The echocardiography machine was Phillips IE 33 (Philips, Zuid-Holland, Netherlands). All patients underwent standard echocardiographic examination performed in the left lateral and supine positions using probe S5-3. Two dimensional (2D) and color Doppler imaging were performed in the standard parasternal and apical positions. Two dimensional, M-Mode, and Doppler measurements were performed according to the American Society of Echocardiography recommendations. The EF was calculated by Simpson's method in 4 chambers and 2 chamber views.⁵

Transmitral flow velocity signals were obtained in the 4 apical-chamber view by placing the pulse Doppler sample at the tips of the valve leaflets. The peak velocity of the early (E) and late (A) filling were measured. Tissue Doppler was acquired with the recommended presets to minimize background noise and enhance the accuracy of the signal. The sample volume was standardized at 10 mm below the septal leaflet margin of the mitral annulus. The frame rate was tuned to more than 150 frames/sec, to enhance the versatility.

The measured TDI parameters were peak systolic velocity (Sa), and the Early (E') and late (Aa) diastolic velocities, guided by the ECG waves. The E/E' ratio defined as the velocity of the mitral inflow pulse wave to the early TDI septal mitral leaflet. All mentioned Doppler indices were obtained during normal expiration. Five cardiac cycles were averaged.

NT-proBNP. Simultaneous NT-proBNP assay was performed after completing the echocardiographic assessment. A venesection was carried out by vacutainer from the antecubital vein through an EDTA bottle. The test was performed in the hormonal laboratory of Salmaniya Medical Complex. Plasma level for NT-proBNP was determined using Elecsys proBNP sandwich immunoassay on an elecsys-2010 (Roche diagnostics, Basel, Switzerland). The cutoff value was 125pg/ml; values below exclude heart failure with high level of certainty.

Statistical analysis was performed using the SPSS version 18 software (SPSS, Chicago, IL, USA). Data was

presented as mean±SD. Bi-variant correlation was used to investigate the potential correlation between variables. The diagnostic ability of the E/E' for predicting the plasma NT-proBNP level was determined by receiving operator characteristics curve (ROC).

Meaningful statistical analysis is achievable once the sample size exceeds 25 subjects. Linear regression analysis was used to evaluate the correlation between the severity of the diastolic dysfunction (the progressive rise of E/E' ratio and the NT-proBNP titer). P-value less than 0.05 was considered statistically significant.

Results. Out of the 70 consecutive patients who were initially enrolled, 22 were excluded. Three had myocardial infarctions, 7 had renal impairment, 5 had systolic dysfunction, 2 had moderate mitral regurgitation, and 5 were in atrial fibrillation. Of the 48 patients studied, 28 were males (mean age 56 years), and 20 females (mean age 62 years). The patients were sorted according to the severity of left-side heart failure into 4 groups of NYHA. Patients in NYHA class I and II were mainly followed in OPD settings; while those in class III and class IV were in-patients (Table 1).

Tissue Doppler and its correlation with pro-BNP. The success of obtaining TDI signals was consistent among all patients regardless of their acoustic window. The medial annular velocity TDI (E/E') maintained a positive correlation with NT-proBNP titer. Interestingly, this correlation was consistent even in patients with normal filling parameters (Figure 1). The correlation coefficient between the septal mitral leaflets E/E' and the NT-proBNP was 0.8 with $p < 0.0001$. Additionally, both E/E' and pro-BNP titer were positively correlated with the clinical severity of left-heart failure (Figures 2 & 3). The predictive ability of the TDI in estimating the NT-proBNP level (the latter being a surrogate marker of diastolic dysfunction severity) can be calculated by creating this simplified equation: NT-proBNP = 93.8 x E/E' - 940.

Table 1 - Patients' characteristics across New York Heart Association (NYHA) groups in 48 patients with systemic hypertension presenting with shortness of breath.

Patient characteristics	NYH1 (n=10)	NYH2 (n=15)	NYH3 (n=11)	NYH4 (n=12)
Age	54±12	55.4±8	60±15	67±8
Male	6 (50)	11 (73)	6 (54)	5 (41)
DM	8 (66)	10 (66)	8 (73)	6 (50)
OPD/Adm	11 O / 1 A	7 O / 8 A	2 O / 9 A	0 O / 12 A
ProBNP	60±52	203±130	896±500	1187±706
E/E'	10±2	15±2.5	17±2	21±3.6

DM - Diabetes mellitus, OPD - outpatient department, Adm - admission to hospital, Pro BNP - pro B-type natriuretic peptide; E/E' - the velocity of the mitral inflow pulse wave to the early tissue Doppler septal mitral leaflet.

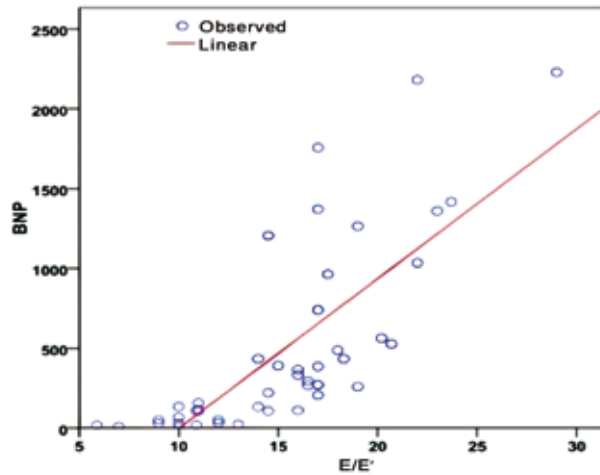


Figure 1 - Linear regression analysis between E/E' and NT pro B-type natriuretic (BNP). E/E' - values were positively correlating with pro BNP levels.

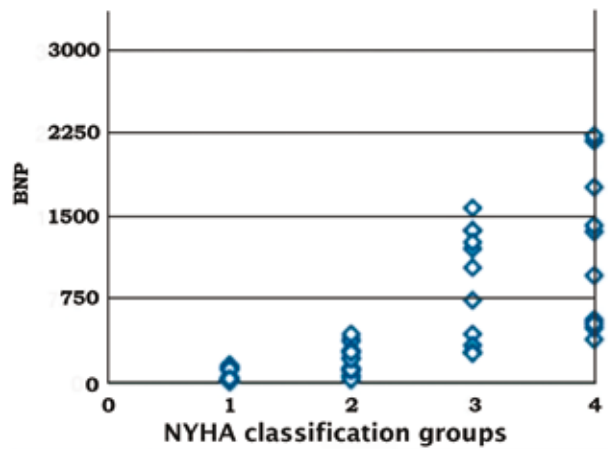


Figure 2 - Distribution of pro B-type natriuretic (BNP) level across 4 NYHA groups. There is a positive correlation between severity of heart failure and levels of pro BNP. E/E' - values were positively correlating with pro BNP levels.

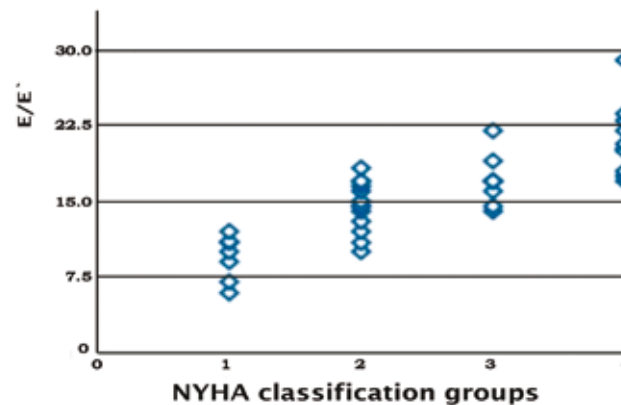


Figure 3 - Distribution of E/E' values across the 4 NYHA groups. There is a positive correlation between severity of heart failure and E/E' values. E/E' - values were positively correlating with pro BNP levels, NYHA - New York Heart Association

Discussion. Diastolic properties of the left ventricle can be studied by pulmonary artery floating catheters or by direct measurement of the left ventricular end diastolic pressure (LVEDP) through retrograde left ventricular cannulation of the aortic valve. The former has gained popularity after the famous paper by Swan et al.⁶ Over the last 25 years, however, its limited cost-effectiveness, safety, and mortality benefit have rendered it under close scrutiny. Its clinical effectiveness has been critiqued among cardiac,⁷ and non-cardiac patients.⁸ Non-invasive modalities (imaging and non imaging) to estimate the diastolic function of the left ventricle are a common clinical challenge confronted by the cardiologist. The value of pro-BNP in diagnosing diastolic dysfunction is well established in recent literature⁹ and incorporated in the current guidelines.¹ Interestingly, its titer correlates well with the degree of diastolic derangements, especially among patients with isolated diastolic dysfunction.¹⁰⁻¹² Over the last decade the E/E' has validated itself as a reliable index estimating the diastolic properties of the left ventricle with a growing level of accuracy.¹³⁻¹⁶ The proposed relationship between tissue Doppler echocardiography and PCWP has been studied by Mekhaela et al in late 1999.¹⁷ They failed to demonstrate a statistical relationship between septal E/E' and the PCWP. A major limitation of their work is the low volume of subjects studied. Being healthy volunteers, subjected to artificial alteration in their left ventricle filling loads, they do not mimic real patients. Almost one year later Jin and Sohn¹³ could estimate the left ventricular pre-A pressure by utilizing E/E'. In this study, the best correlation was shown in patients with normal EF where the higher E/E' ratio correlated well with pre-A left ventricular pressure.¹³ Within almost the same time frame, Rivas-Gotz et al¹⁸ investigated the tissue Doppler imaging's ability to estimate the pulmonary capillary in dogs and humans. Tissue Doppler imaging has demonstrated a great potentiality in estimating the left ventricle filling pressure, particularly among patient with normal EF.¹⁸ In 2002, Pozzoli et al,¹⁹ published a comprehensive review about non-invasive estimation of left ventricle filling pressure by echocardiography and illustrated different equations that incorporate E/E' ratio to quantify the filling pressure. As this modality gained more popularity, clinical researchers started to testify its validity utilizing it in estimating left ventricle filling pressure among more heterogenous groups of patients. Recently, Mullens et al,²⁰ assessed the reliable cogency of tissue Doppler parameters among patients with advanced systolic heart failure patients. Their disappointing results negated the initial ability of tissue Doppler to diagnose high filling pressure.²⁰ This study initiated a major dispute and led people to start questioning the diagnostic accuracy of tissue Doppler filling pressure estimation. When reviewing

the patient's clinical data together with their inclusion criteria, one has to use extra caution in interpreting their results, to avoid the perception of an inaccurately conveyed message. Including patients with significant mitral regurgitation and dilated cardiomyopathy on cardio-resynchronization therapy (CRT) markedly jeopardizes the reproducibility of the E/E'. Among both groups, the distorted anatomy, left ventricular geometry, and dilatation, compromises the versatility of the TDI.²¹ The uncertainty regarding its rule among patients with advanced systolic heart failure inspired further studies asserting its reliance. In 2010, Malfatto et al²² could support the rule of TDI E/E' in estimating the diastolic dysfunction among patients with severe systolic heart failure. The results, however, have to be vigilantly analyzed as their inclusion criteria were better defined, even though patients with CRT for more than 6 months were included.²² The contrast should motivate further studies defining its actual standing point, even though the scanty literature supports its rule in these patients if utilized within a well-defined clinical and echocardiographic context.

In our study, by applying strict inclusion criteria and excluding patients documented in previous studies that could alter the diagnostic accuracy of the NT-proBNP and TDI, we could stress the tight relationship between E/E' and left ventricular filling pressure among patient with normal EF. Our own data contributed to the accumulated evidence that E/E' of the septal leaflet, if properly utilized within the well-defined clinical context, can stratify the degree of the diastolic dysfunction with great accuracy.¹⁴ In this article, we utilized the NT-proBNP titer as a marker of diastolic dysfunction severity. Simultaneous detailed diastolic assessment by TDI was commenced. The studied patients were hypertensives with their main complaint being shortness of breath. The range of their NYHA was sub-classified into 4 groups (Table 1). The reproducibility of the TDI E/E' was consistent among the studied group. The feasibility and the affordable acquisition of the TDI images (despite the variable acoustic window quality) is a unique feature offered by this technique unlike other parameters such as pulmonary vein reversal flow. Our data coincided with Sohn et al,¹³ where the E/E' levels were consistent regardless of the mitral inflow.¹³ The echocardiographic degree of the diastolic derangement had a powerful relationship with NT-proBNP. Interestingly, the non-conclusive accuracy of E/E' between the range of 8-15 has not been encountered. We believe our inclusion criteria, where only hypertensive patients (abnormal heart) were studied, helped to overcome the previous obstacles faced by others. A major limitation of the E/E' is its poor correlation with pulmonary capillary wedge pressure in normal individuals. The evidence that tissue Doppler indices can vary substantially across

a wide range of filling pressures in normal individuals convinced us to preclude such subjects from the study.²³ With our regression equation we could estimate the NT-proBNP (severity of diastolic dysfunction) = $93.8 \times E/E' - 940$. This simplified equation, which can easily be applied in clinical practice, provides quantitative assessment of the left ventricular filling pressure with high reliability ($r=0.8$) and $p=0.000$.

Lacking a simultaneous invasive assessment of the diastolic function can be considered a limitation in our trial; however, the supporting evidence that NT-proBNP is a reliable marker of high specificity for predicting diastolic dysfunction severity balances that limitation. Furthermore, subjecting our patients to pulmonary artery wedge catheterization or left sided LVEDP measurement with no clinical indication would raise a major ethical concern.

In conclusion, our study boosts the collective literature supporting the clinical rule of tissue Doppler imaging in ascertaining the severity of diastolic dysfunction. Results afforded by our study can be considered highly reliable, as the study was conducted in a community hospital reflecting patients encountered in reality. Steadiness of the TDI results can only be maintained if the application is used with acute awareness of which clinical variables that weaken its interpretation are omitted. In other words, to optimize the utility of the TDI, its limitation has to be well-comprehended, thereby the authentic capability is not overestimated.

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