Velocity Vector Imaging and NT-ProBNP to Quantify Systolic Function and Intraventricular Mechanical Dyssynchrony to Predict Cardiac Outcome in Patients with Chronic Heart Failure

Faida O1, Oteh M1*, A Lattif M2, Fadillah AW1

1 Medical department-Cardiology unit, UKM medical center, Jalan Yaacob Latiff, Bandar Tun Razak, Cheras 56000 Kuala Lumpur, Malaysia
2 Cyberjaya University College of Medical Sciences, Unit No 2 Street Mall 2, 63000 Cyberjaya, Selangor Darul Ehsan, Malaysia

* Corresponding Author: Prof. Madya Dr Oteh Maskon
Head of Cardiology Unit, Department of Medicine
Universiti Kebangsaan Malaysia, medical Center
Jalan Yaacob Latiff, Bandar Tun Razak, Cheras 56000 Kuala Lumpur, Malaysia
Tel: +60-3-91733333 | H/P +60193217391

Abstract

Aims: This study sought the prognostic value of velocity vector imaging parameters and NT-proBNP level as independent predictors for the outcome in HF and examining the utility of NT-proBNP level compared to multiple VVI parameters which have not been clarified.

Methods and Results: 108 patients with heart failure underwent speckle tracking with (VVI), systolic function and mechanical dyssynchrony parameters correlating with NT-proBNP level and examined their influence on outcome. Average (velocity, strain, strain rate, displacement) ejection fraction, and intraventricular mechanical dyssynchrony based on: SD of time to peak velocity, SD of time to peak displacement and maximal temporal difference of time to peak systolic velocity were significantly associated with clinical events. 948pg/ml NT-pro BNP cutoff value reliable for prediction of cardiac events. In multivariate analysis was revealed that NT- proBNP and strain rate were identified as the independent predictors for cardiac events. VVI parameters compared with NT-proBNP levels, significant correlations were found between NT-proBNP level and longitudinal velocity (R = -0.650, P< 0.0001), displacement (R = -0.646, P< 0.0001), strain (R = 0.681, P< 0.0001), strain rate (R = 0.691, P< 0.0001) and ejection fraction(R = -0.807, P< 0.0001). Additionally, log NT-proBNP levels correlated moderately with systolic dyssynchrony (Ts-SD) and small correlation with (Ts-diff) but statistically significant. In multiple linear model revealed that the ejection fraction was the strongest predictor of NT- proBNP level (Beta = - 0.907, P< 0.0001).
Conclusions - Longitudinal mechanical functions’ parameters assessed by VVI have the ability to further identify patients at higher risk of CV events. Use NT-proBNP cutoff value of 948pg/ml is easy and reliable for prediction of mechanical dysfunction and aid identification of patients at highest risk for future cardiac events.

Key words: Chronic Heart Failure; vector velocity imaging, left ventricular dyssynchrony, NT-proBNP

Introduction

Heart failure constitutes a major health problem in the world and despite recent advances in pharmacological therapy often debilitating. With the aging of the population, the prevalence of CHF is expected to increase. Approximately third of the patients with heart failure demonstrate intraventricular conduction abnormalities. These conduction abnormalities are usually in the form of complete left bundle branch block (LBBB) or intraventricular conduction delays and are related to increased morbidity and mortality.

Left ventricular dyssynchrony has a deleterious effect on hemodynamic function and prognosis in patients with chronic heart failure. In addition, correction of dyssynchrony has been shown to improve immediate hemodynamics, symptoms, quality of life, exercise tolerance, and survival in patients with chronic heart failure.

Chronic heart failure (CHF) is currently recognized as a clinical syndrome occurring not only as a result of mechanical dysfunction of the ventricles, but also due to complex molecular, endocrine, neuroendocrine, and inflammatory changes. Neurohormonal activation plays a fundamental role in the onset and progression of heart failure and the use of biochemical markers as prognostic indicators in heart failure have expanded in the last decade. NT-proBNP has been studied as a biomarker of severity and prognosis of CHF in small studies and shown to be very reliable. The level of NT-proBNP remained predictive of death and of the combined end point of death and hospitalization.

Ultrasound imaging of the heart continues to play an important role in diagnosis and management of patients with cardiovascular diseases. Recent advances in ultrasound technology and introduction of newer imaging modalities have enabled improved assessment of left ventricular myocardial function and mechanical synchrony. Tissue Doppler imaging and 2-dimensional speckle tracking allow more objective quantification of myocardial mechanic in the form of tissue velocities, displacement, strain, strain rate and mechanical dyssynchrony assessment.

We performed this study to assess the prognostic value of multiple parameters derived from vector velocity imaging (VVI) and NT-proBNP level for predicting adverse cardiac events in patients with chronic heart failure, and examining the utility of NT-proBNP level compared to multiple VVI parameters.
Patients and Methods

The study enrolled 150 patients with systolic and diastolic heart failure, presenting to the Cardiology Department of the University Kebangsaan Malaysia (UKM) Medical Center, have signs and symptoms according to European society of cardiology for heart failure (ESC clinical classification for HF).

Patients were recruited according to inclusion and exclusion criteria; patients with severe renal failure (serum creatinine >5mg/dl), no sinus rhythm, MI within 3 months, HF caused by cor pulmonale, congenital heart disease, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, ventricular thrombus were excluded. All patients gave their written informed consent to take part in the study. Among the 150 patients initially enrolled in the study, 6 patients passed away, 28 patients withdrew their consents and 7 patients did not answer at the time of examination and one excluded due to inadequate quality of imaging, leaving 108 patients eligible for analysis. The study was approved by the local ethics committee of University Kebangsaan Malaysia.

NT-proBNP measurement

At the time of echocardiographic examination, a blood sample was collected into tubes containing- separating gel, processed, and frozen at – 80 Ċ for later measurement of NT-proBNP using a commercially available automated immunoassay (Cobas e 411 analyzers, Roche Diagnostics).

Echocardiography

Recordings were made with the patient in the supine left lateral position during quiet respiration. Using an Acuson Sequoia c512 ultrasound system (Siemens, MountainView, CA) and 4V1c transthoracic transducer. The left ventricular ejection fraction was assessed by the biplane Simpson’s rule.16,17

For VVI analysis, Digital cine loops were obtained at frame rates of 50 - 70 Hz per single cardiac beat on apical 4-chambers, 2-chambers, and 3-chambers views and the 2D images were acoustically captured. The secured images were saved in a MO disk for offline analysis. With the use of an offline analysis program (Synco US Workplace 3.0, Simence; Acuson), the contour of endocardium was manually traced on the saved images before the analysis was performed. The tracing was performed repeatedly several times for the most appropriate endocardial contour.

In the septum, lateral, inferior, anterior, antero-septal and posterior walls of the LV, the basal and mid segments, were subjected to the measurement for Longitudinal velocity, strain, strain-rate, displacement, and apical segments were prospectively excluded because of the relatively low velocity movement of the left ventricular apex.10,16,18
All of the echocardiographic parameters (velocity, strain, strain rate and displacement) which were obtained from VVI were measured by a single investigator from three cardiac cycles, and then averaged, which was performed twice. Dyssynchrony indexes were measured with the same B-mode speckle tracking software that angle independency and identifies cardiac motion by tracing along the endocardial border, the semiautomated tracking algorithm outlined the myocardium from frame to frame throughout the cardiac cycle, and velocity vectors, overlaid onto the B-mode image, were displayed with the direction and relative speed of the tissue. Tracking quality was verified for each segment with manual adjustment if necessary, provided velocity vector profiles of myocardial motion.

Dyssynchrony was defined as the maximal difference in peak longitudinal velocity at the basal and mid segments in opposing walls per view and time to regional peak velocity (Tvel), strain (Tst), strain rate (Tsr) and displacement (Td) were measured during the ejection phase, and the SDs between all 12 segments were used as a measure of dyssynchrony.  

Statistical Analysis
Data were analyzed using the statistical software (IBM SPSS Statistics version 20).

Categorical data were expressed as numbers (%) and compared by using chi-square test. Data were tested for normality. Parametric data were expressed as mean ± standard deviation and compared by using 2-tailed student t-test. Non-parametric data were reported as median and 25th and 75th percentiles and compared by Mann Whitney U test. Log-transformation and square were used to achieve normality in distribution.

Univariable simple linear regression analysis was used to determine correlation between echocardiographic parameters and age as independent variables with log NT-proBNP levels as dependent variables. Multivariable linear regression analysis model was used to determine correlations between variables as a model. Logistic regression analysis model was used to determine independent predictors of primary end points at the end of one year follow up.

Receiver-operating characteristic (ROC) curve was performed to calculate the optimal cutoff values with its sensitivity and specificity for predicting the primary end points. P value of < 0.05 level was considered to be statistically significant.

Results

Patient’s characteristics
For the 108 patients included in the study, mean age was 59 ± 10 years (range 31 - 81 years), there were 20 female (18.5%) and 88 male (81.5%), hypertensive was 74/108
(68.5%) diabetes mellitus was 46/108 (42.6%), coronary artery disease was 85/108 (78.7%), dyslipideamia was 79/108 (73.1%).

Mean left ventricular ejection fraction (LVEF) was 38.10 ±13.27, of the 23/108 patient (21.5%) with LVEF ≥50% and 85/108 patient (78.5%) with LVEF < 50%.

Baseline clinical and echocardiographic data of the patients are summarized in Table 1.

**NT-proBNP level**

The median NT-proBNP level among the 108 patients with systolic and diastolic heart failure in this study was 709.60 pg/mL (range 5–17100 pg/ml; inter-quartile range (IQR) = 197.85–2116.50 pg/mL).

**Correlation of NT-proBNP level and vector velocity imaging parameters (VVI)**

Simple linear regression analysis (having only one predictor) was performed between log NT-proBNP levels as dependent parameter and age and other independent parameters of cardiac function and mechanical LV dyssynchrony indices derived from VVI were shown in Table 2. There was a strong, negative and highly significant correlation between ejection fraction and log NT-proBNP level (R = -0.807, P< 0.0001). $R^2 = 0.651$ which implies that 65% of NT-pro BNP variations is explained by the EF. No correlation was found between age and log NT-proBNP level.

The correlation between the parameters derived from VVI (average longitudinal velocity, longitudinal displacement) and log NT-proBNP level were strong, negative, and highly significant ($R = -0.650, P< 0.0001$ and $R= -0.646, P<0.0001$) respectively. $R^2 = 0.423$ and 0.417, which implies that 42.3% and 41.7% of NT-pro BNP variations is explained by the longitudinal velocity and displacement respectively. The correlation between average longitudinal Strain, strain rate and log NT-proBNP level were strong and highly significant ($R = 0.681, P< 0.0001$ and $R = 0.691, P< 0.0001$) respectively. $R^2 = 0.464$, 0.478, which implies that 46.4%, 47.8% of NT-pro BNP variations is explained by the longitudinal strain and strain rate respectively. Additionally, log NT-proBNP levels correlated moderately with systolic dyssynchrony Tv-SD ($R= 0.360, P< 0.0001$) and small correlation with systolic dyssynchrony Tv-diff ($R= 0.276, P< 0.004$, but statistically significant. Fig 1a b c d e.

This study revealed that there were no relation between NT-pro BNP level and age, septal to lateral delay, antero-septal to posterior delay and standard deviation of time to peak systolic strain, strain rate and displacement.

Analysis with a multiple linear regression model to confirm the important variables correlating with NT-proBNP, revealed that NT-proBNP levels to be independently related to Age, ejection fraction, longitudinal systolic velocity, strain rate, maximal temporal difference of time to peak systolic velocity, septal to lateral delay were
significantly correlated to NT-proBNP levels. Table 2. Adjusted $R^2=0.75$, $p<0.0001$, which implies that 75% of variability in NT-proBNP is explained by these independent variables in this model, and the ejection fraction was the strongest predictor of NT-proBNP level ($\text{Beta} = -0.907$, $P<0.0001$).

**NT-proBNP and cardiac outcome**

At one year, 36 of 108 patients (33.3%) reached the primary end point; there were 23 of 36 (63.88%) hospitalizations for heart failure deterioration and 13 of 36 (36.12%) cardiac death. Significant characteristics of patients with and without cardiac events at one year are listed in Table 3. Patients with high baseline NT-proBNP were more prone to cardiac events than those with low NT-proBNP.

In the ROC curve analysis a 948 pg/mL NT-proBNP cutoff value revealed sensitivity 75% and specificity of 29%, for the prediction of incident cardiac events. The AUCROC in predicting cardiac events was found to be 0.778 with high discrimeny power for NT-proBNP.

NT-proBNP with $p$ value was 0.037 and strain rate with $P$ value was 0.029, were identified as the independent predictors of cardiac events at the end of 12 months respectively.

**Vector velocity imaging (VVI) parameters analysis**

The results of cardiac function and mechanical LV dyssynchrony indices assessed by VVI are displayed in Table 1. parameters which were measured from 12 segments and then averaged, such as cardiac velocity, strain, strain rate and displacement; there were significant difference ($p<0.0001$) in these parameters between the two groups of clinical events.

The LV intraventricular delay based on standard deviation of time to peak systolic velocity ($Tv-SD$) with $p$ value (0.006), time to peak systolic displacement($Td-SD$) with $p$ value (0.02) and maximal time difference between 12-segments ($Tv$-diff) with $p$ value (0.03) were significant. But the LV intraventricular delay based on standard deviation of time to peak systolic strain($Tst-SD$) with $p$ value (0.186) and time to peak systolic strain rate ($Tsr$-SD) with $p$ value (0.306)] were statistically not significant. S-L delay and AS-P delay were provided no significant differences between the two groups of clinical events.

Clinical and echocardiographic data between two groups are summarized in (Table 3).

**VVI parameters and Cardiac outcome**

Clinical and echocardiographic parameters were investigated for their predictive value for clinical events by bivariate and multivariate analysis.
In bivariate analysis, all categorical variables were found statistically not significant, cardiac function such as: average( velocity, strain, strain rate, displacement) , ejection fraction, NT-pro BNP and intraventricular mechanical dyssynchrony based on Tv-SD, Td-SD and Ts-diff, were significantly associated with development of clinical events with p values (p=0.0001, p=0.0001, p=0.0001, p=0.0001, p= 0.0001, p=0.0001, p=0.006, p=0.02,0.03) respectively Table 3.

In multivariate logistic regression analysis was revealed that all these parameters were entered in the model which predicts 37% of variation in clinical events at the end of 12 months was explained by the model. The overall accuracy of this model to predict subjects having clinical events was 73% with 42% sensitivity and 89% specificity. Positive predictive value (PPV) was 65.2% and negative predictive value (NPV) was 75.3%. The receiver operator characteristic (ROC) curves were constructed to determine the optimal cutoff value for NT-pro BNP, average strain, average strain rate and Ts-SD Fig. 2 a b c d for predicting clinical events at one year, the overall sensitivity and specificity of different parameters using ROC curves were compared.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cut-off</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP</td>
<td>948</td>
<td>0.778</td>
<td>75%</td>
<td>29%</td>
</tr>
<tr>
<td>Average Strain</td>
<td>-8.62</td>
<td>0.774</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Average Strain rate</td>
<td>-0.53</td>
<td>0.767</td>
<td>78%</td>
<td>63%</td>
</tr>
<tr>
<td>Tv - SD</td>
<td>62.24</td>
<td>0.653</td>
<td>64%</td>
<td>54%</td>
</tr>
<tr>
<td>Tv - diff</td>
<td>184.50</td>
<td>0.611</td>
<td>56%</td>
<td>47%</td>
</tr>
<tr>
<td>Td - SD</td>
<td>87.35</td>
<td>0.620</td>
<td>59%</td>
<td>56%</td>
</tr>
</tbody>
</table>

**Discussion**

Two-dimensional speckle tracking has enhanced the ability to assess regional and global myocardial properties noninvasively because of its angle independence, which overcomes the limitations of tissue Doppler imaging. The specific method used in this analysis, velocity vector imaging has been validated. Moreover, these methods allow retrospective analysis of echocardiographic images obtained under standard conditions and do not require collection of raw data.

Early two-dimensional strain and SR images based on the speckle tracking echocardiographic (STE) technique were developed to overcome the angle dependence of DTI. In the past, DTI and STE have been time consuming, and the high variability in DTI, as well as the computational complexity and immature algorithm presented by early STE, limited their application to the human heart. Recently, the STE technique has been improved and used effectively in the study of cardiac function.

VVI is an advanced echocardiographic method that is based on STE. In gray scale images, interference by backscattered ultrasound from neighboring structures results in a random, speckled pattern.
This gives each small area a unique pattern that remains relatively constant from one frame to the next. With the optimized pattern-matching algorithm, VVI can accurately track these speckles frame by frame, and through reconstructing the deformation and motion, the motion of flow and tissue can be analyzed. The advantage of VVI is that it is self-updating. Special reference settings are applied, including valvular annulus, chamber borders and tissue motion, as well as the relatively static reference point provided by the software. All of the above make the tracking process more precise. VVI is faster than conventional STE, and obtaining each patient’s parameters may take approximately 5 min, which is less time than in routine STE study.

LV systolic function is commonly considered normal if the GEF and FS are normal. But the GEF and FS only reflect the global cardiac contractile function and do not take the regional systolic abnormality into consideration.

In the present prospective study, we demonstrated that global longitudinal functions’ parameters of left ventricular systolic dysfunction (velocity, displacement, strain and strain rate) assessed by VVI is an independent predictors of adverse cardiac events (cardiac death and hospitalization for worsening heart failure) intraventricular mechanical dyssynchrony based on Tv-SD, Td-SD and Tv-diff. may contribute to adverse prognosis and development of adverse cardiac events, that is independent of measures of ventricular function. Several studies are recognized mechanical dyssynchrony as an independent predictor of cardiac events and worse survival in patients with heart failure.

We found that analyses of Tst or Tsr and S-L delay or AS-P delay were not significantly different with respect to predictive value, although Tsr has some potential advantages in that it measures the timing of true myocardial contractile motion rather than simply passive myocardial motion.

This study utilized the previously proven predictor biochemical marker NT-proBNP and has been adjusted for clinical and echocardiographic covariates in multivariate regression and found that NT-proBNP and strain rate was independent predictors of adverse cardiac events. Nevertheless, it should be noted that these methods are cumbersome and are not recommended as a method to assess synchrony but were used in this analysis as a tool to understand the pathophysiological link between synchrony and outcome independently of global or regional systolic function. However, this study was the first study provided further data on correlations between NT proBNP level and longitudinal mechanic functions’ parameters derived from VVI (velocity, displacement, strain, strain rate) and intra-LV mechanical dyssynchrony based on (Tv-SD, Td- Tv-diff.) that have been shown significant correlations.

After adjustment for clinical and VVI parameters we found age, EF, velocity, strain rate, Tv-diff. and S-L delay were correlate with NT-proBNP.

The results of this study have several important implications.

First, independent of the LVEF and NT-proBNP, longitudinal mechanic function of LV derived from VVI (velocity, displacement, strain, strain rate) and intra-LV mechanical
dyssynchrony based on (Tv-SD, Td-SD, Tv-diff.) influence the outcome of heart failure patients and have a much higher risk of worsening and a severe prognosis of mortality.

Second, the presence of intra-LV mechanical dyssynchrony based on (Tst-SD, Tsr-SD, S-L delay, AS-P delay) does not influence the outcome of heart failure patients.

Third, significant correlations were found between NT-proBNP as independent predictor and VVI parameters (velocity, displacement, strain, strain rate, Tv-SD, Tv-diff.).

**Conclusion**

VVI is an effective angle independent echocardiographic method that can be used to assess global and regional myocardial dysfunction in patients with heart failure. VVI recordings and NT-proBNP level have the ability to further identify patients at higher risk of death, development of clinically overt HF. In addition, these prognostic parameters may select patients who are potential responders to non-pharmacologic HF treatment; however, further studies need to be done to introduce this technique widely in clinical practice. The implications of these research findings are breaking a new ground in heart failure monitoring and therapy, so the earlier treatment can be administrated to high risk patients as HF management program.

**Limitation**

This study has several important limitations.

First, although B-mode–based speckle tracking techniques may be more robust than Doppler-based methods, a number of factors can reduce data quality, including lateral resolution in the far field, out-of-plane motion, and image dropout, a high-quality image is required, like all quantitative echocardiographic methods and special care must be taken to draw the outline of an ROI. Second, the deformation of myocardium is three-dimensional, but currently, VVI only offers a two dimensional plane.

Third, patients with systolic and diastolic HF were included in this study.

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**References**


4. Bader, Hugues; Garrigue, Stephane; Lafitte, Stephane; Reuter, Sylvain; Jaïs, Pierre; Haïssaguerre, Michel; Bonnet, Jacques; Clemency, Jacques; Roudaut, Raymond. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol. 2004;43(2):248-56.

5. Penicka, Martin; Bartunek, Jozef; Lang, Otto; Medilek, Karel; Tousek, Petr; Vanderheyden, Marc; De Bruyne, Bernard; Maruskova, Michaela; Widimsky, Petr. Severe left ventricular dyssynchrony is associated with poor prognosis in patients with moderate systolic heart failure undergoing coronary artery bypass grafting. J Am Coll Cardiol. 2007;50(14):1315-23.

6. Cho, Goo-Yeong; Song, Jae-Kwan; Park, Woo-Jung; Han, Sung-Woo; Choi, Seung-Hyuk; Doo, Young-Cheoul; Oh, Dong-Jin; Lee, Yung. Mechanical dyssynchrony assessed by tissue Doppler imaging is a powerful predictor of mortality in congestive heart failure with normal QRS duration. J Am Coll Cardiol. 2005;46(12):2237-43.

7. Abraham, William T; Fisher, Westby G; Smith, Andrew L; Delurgio, David B; Leon, Angel R; Loh, Evan; Kocovic, Dusan Z; Packer, Milton; Clavell, Alfredo L; Hayes, David L; Ellestad, Myrvin; Trupp, Robin J; Underwood, Jackie; Pickering, Faith; Truex, Cindy; McAtee, Peggy; Messenger, John; Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845-53.

8. Bristow, Michael R; Saxon, Leslie A; Boehmer, John; Krueger, Steven; Kass, David A; DeMarco, Teresa; Carson, Peter; DiCarlo, Lorenzo; DeMets, David; White, Bill G; DeVries, Dale W; Feldman, Arthur M. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350(21):2140-50.


10. Yu, Cheuk-Man; Chau, Elaine; Sanderson, John E; Fan, Katherine; Tang, Man-Oi; Fung, Wing-Hong; Lin, Hong; Kong, Shun-Ling; Lam, Yui-Ming; Hill, Michael R S; Lau, Chu-Pak. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation. 2002;105(4):438-45.


12. Hartmann, Franz; Packer, Milton; Coats, Andrew J S; Fowler, Michael B; Krum, Henry; Mohacsi, Paul; Rouleau, Jean L; Tendera, Michal; Castaigne, Alain; Anker, Stefan D; Amann-Zalan, Ildiko; Hoersch, Silke; Katus, Hugo A. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol


14. Song, Bong Geun; Jeon, Eun Seok; Kim, Yong Hoon; Kang, Min Kyung; Doh, Joon Hyung; Kim, Phil Ho; Ahn, Seok Jin; Oh, Hye Lim; Kim, Hyun-Joong; Sung, Ji Dong; Lee, Sang Chol; Gwon, Hyeon Cheol; Kim, June Soo; Kim, Duk-Kyung; Lee, Sang Hoon; Hong, Kyung Pyo; Park, Jeong Euy; Lee, Soo Youn; Lee, Jong Koo. Correlation between levels of N-terminal pro-B-type natriuretic peptide and degrees of heart failure. Korean J Intern Med. 2005;20(1):26-32.


18. Sutton, MG; Plappert, T; Abraham, WT; Smith, AL; DeLurgio, DB; Leon, AR; Loh, E; Kocovic, DZ; Fisher, WG; Ellestad, M, Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107:1985-90.

19. Yu, Cheuk-Man; Fung, Jeffrey Wing-Hong; Zhang, Qing; Chan, Chi-Kin; Chan, Yat-Sun; Lin, Hong; Kum, Leo C C; Kong, Shun-Ling; Zhang, Yan; Sanderson, John E. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation. 2004;110(1):66-73.


21. Amundsen, Brage H; Helle-Valle, Thomas; Edvardsen, Thor; Torp, Hans; Crosby, Jonas; Lyseggen, Erik; Støyle, Asbjørn; Ihlen, Halfdan; Lima, João A C; Smiseth, Otto A; Slordahl, Stig A. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol. 2006;47(4):789-93.

22. Reant, Patricia; Labrousse, Louis; Lafitte, Stephane; Bordachar, Pierre; Pillois, Xavier; Tariosse, Liliane; Bonoron-Adele, Simone; Padois, Philippe; Deville, Claude; Roudaut, Raymond; Dos Santos, Pierre. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. J Am Coll Cardiol. 2008;51(2):149-57.

23. Vannan, Mani A; Pedrizzetti, Gianni; Li, Peng; Gurudevan, Swaminathan; Houle, Helene; Main, Joan; Jackson, John; Nanda, Navin C. Effect of cardiac resynchronization therapy on longitudinal and circumferential left ventricular mechanics by velocity vector imaging:


29. Langeland, Stian; D'hooge, Jan; Wouters, Patrick F; Leather, H Alex; Claus, Piet; Bijnens, Bart; Sutherland, George Ral. Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. Circulation. 2005;112(14):2157-62.


Table 1: Baseline Clinical and Echocardiographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Study Sample (n=108)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>59.47 (±10.60)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>88 (81.5%)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>20 (18.5%)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>74 (68.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>46 (42.6%)</td>
</tr>
<tr>
<td>CAD, %</td>
<td>85 (78.7%)</td>
</tr>
<tr>
<td>Dyslipideamia, %</td>
<td>79 (73.1%)</td>
</tr>
<tr>
<td>Median NT- pro BNP (pg/ml; IQR)</td>
<td>709.60 (19785-2116.50)</td>
</tr>
<tr>
<td>Echocardiographic variables</td>
<td></td>
</tr>
<tr>
<td>LVEF %</td>
<td>38.10 (±13.28)</td>
</tr>
<tr>
<td>systolic velocity, cm/s (Median)</td>
<td>1.92 (1.3-2.6)</td>
</tr>
<tr>
<td>Average strain, %</td>
<td>- 9.77 (±4.99)</td>
</tr>
<tr>
<td>Average strain rate, s^{-1}</td>
<td>0.56 (±0.27)</td>
</tr>
<tr>
<td>Average Displacement, cm/s</td>
<td>3.81 (±1.82)</td>
</tr>
<tr>
<td>Tv-SD (ms)</td>
<td>62.31 (±21.64)</td>
</tr>
<tr>
<td>Tv-diff (ms)</td>
<td>187.27 (±59.88)</td>
</tr>
<tr>
<td>Tst-SD (ms)</td>
<td>121.24 (±65.22)</td>
</tr>
<tr>
<td>Tstr-SD (ms)</td>
<td>68.86 (±27.13)</td>
</tr>
<tr>
<td>Td-SD, ms (Median)</td>
<td>87 (53.5-130.15)</td>
</tr>
<tr>
<td>S-L delay, ms (Median)</td>
<td>50.5 (31-119.5)</td>
</tr>
<tr>
<td>As-P delay, ms (Median)</td>
<td>41 (0 - 83.5)</td>
</tr>
</tbody>
</table>

Tv-SD, time to peak systolic velocity; Tv-diff, maximal temporal difference of Tv; Tst-SD, time to peak systolic strain; Tsr-SD, time to peak systolic strain rate; Td-SD, time to peak systolic displacement; S-L, septal to lateral delay; As-P, anteroseptal to posterior delay.
<table>
<thead>
<tr>
<th></th>
<th>Univariate linear regression</th>
<th></th>
<th>Multiple linear regression</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>R²</td>
<td>P</td>
<td>β</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.005</td>
<td>0.00</td>
<td>0.959</td>
<td>0.224</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.807</td>
<td>0.651</td>
<td>0.0001</td>
<td>-0.907</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
| Strain         | 0.681 | 0.464 | 0.0001
| Strain rate    | 0.691 | 0.478 | 0.0001 | -0.238 | 0.026 |
| Displacement   | -0.646 | 0.417 | 0.0001
| Velocity       | -0.650 | 0.423 | 0.0001 | -0.262 | 0.002 |
| S-L delay      | 0.044 | 0.002 | 0.649 | 0.232 | 0.0001 |
| As-P delay     | 0.080 | 0.006 | 0.409
| Tv-SD          | 0.360 | 0.130 | 0.0001
| Tv-diff        | 0.276 | 0.076 | 0.004 | 0.124 | 0.026 |
| Tst-SD         | 0.181 | 0.033 | 0.061
| Tsr-SD         | 0.135 | 0.018 | 0.165
| Td-SD          | 0.161 | 0.026 | 0.095

For abbreviations see Table 1
Table 3: Clinical and Echocardiographic Parameters between Two Groups

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>No (n = 72)</th>
<th>Yes (n = 36)</th>
<th>pValue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60 ±11</td>
<td>57± 9</td>
<td>0.242</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>75</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>64.8</td>
<td>35.2</td>
<td>0.381</td>
</tr>
<tr>
<td>Ischemic origin (%)</td>
<td>64.7</td>
<td>35.3</td>
<td>0.406</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>60.9</td>
<td>39.1</td>
<td>0.271</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>67.6</td>
<td>32.4</td>
<td>0.770</td>
</tr>
<tr>
<td>Dyslipideamia (%)</td>
<td>65.8</td>
<td>34.2</td>
<td>0.759</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>840.5 ±993.5</td>
<td>3614.6 ±4520.9</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Echocardiographic variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>42.2 ± 12</td>
<td>29.9 ± 11</td>
<td>0.0001</td>
</tr>
<tr>
<td>systolic velocity cm/s</td>
<td>2.3 ± 1</td>
<td>11.5 ± 0.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average strain cm/s</td>
<td>-11.34 ± 5</td>
<td>-6.7 ± 3.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average strain rate cm/s</td>
<td>-0.64 ± 27</td>
<td>-0.40 ± 0.19</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average Displacement cm/s</td>
<td>4.4 ± 1.8</td>
<td>2.7 ± 1.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ts-SD (ms)</td>
<td>57.9 ± 18.4</td>
<td>71.19 ± 24.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Ts-diff (ms)</td>
<td>178.14 ± 56.3</td>
<td>205.5 ± 62.2</td>
<td>0.030</td>
</tr>
<tr>
<td>Tst-SD (ms)</td>
<td>115.3 ± 64.2</td>
<td>133 ± 66.5</td>
<td>0.186</td>
</tr>
<tr>
<td>Tstr-SD (ms)</td>
<td>67.7 ± 29.6</td>
<td>71.2 ± 21.5</td>
<td>0.306</td>
</tr>
<tr>
<td>Td-SD (ms)</td>
<td>92.8 ± 56.7</td>
<td>114.9 ± 64.5</td>
<td>0.020</td>
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<tr>
<td>S-L delay ms</td>
<td>64.6</td>
<td>86.8</td>
<td>0.106</td>
</tr>
<tr>
<td>As-P delay ms</td>
<td>54.7</td>
<td>61.7</td>
<td>0.599</td>
</tr>
</tbody>
</table>

For abbreviations see Table 1
**Figure 1:** Scatter plots showing the correlation between log NT-proBNP level and (A) ejection fraction; (B) longitudinal strain; (C) longitudinal strain rate; (D) longitudinal displacement; (E) longitudinal velocity.
B

\[ R = 0.681 \]
\[ P = 0.0001 \]

C

\[ R = 0.691 \]
\[ P = 0.0001 \]
Figure 2: Receiver-operator characteristic curves analysis (AUROC) of NT-proBNP, Strain rate, Strain, Tv-SD, in predicting cardiac events and determine the optimal cut-off value of (A) NT-proBNP. (B) Strain (C) rate Strain. (D) Tv-SD.
**B**

ROC Curve

AUROC = 0.767
Cutoff value = -0.53 cm/s

**C**

ROC Curve

AUROC = 0.774
Cutoff value = -8.62 cm/s
D

AUROC = 0.653
Cutoff value = 62.24 ms