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CLINICAL & BASIC RESEARCH

Systolic Function and Intraventricular Mechanical Dyssynchrony Assessed by Advanced Speckle Tracking Imaging with N-terminal Prohormone of Brain Natriuretic Peptide for Outcome Prediction in Chronic Heart Failure Patients

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الوظيفة الانقباضية وخلل التزامن الميكانيكي داخل البطين متابعة بتقنية التنقيط بالموجات الصوتيه للقلب مع بروهرمون ناتيروتك ببتايد للتنبؤ بالنتائج لمرضى فشل القلب المزمن

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الملخص: الهدف: هدف هذه الدراسة هو تقييم الوظيفة الانقباضية الطولية و التزامن الميكانيكي داخل البطين و ذلك باستخدام دلائل مشتقة من تقنية حديثة لجهاز الموجات الصوتيه للقلب وعلاقتها بتركيز الشطر الأميني من بروهرمون الناتيروتك ببتايد (NT-proBNP) ولدراسة تـأثيرهـا على الأحداث المستقبلية لفشل عضلة القلب بعد سنة من المتابعة الإكلينيكية و التي لم توضح بعد في دراسات أخرى. **الطريقة:** تم استخدام التقنية الحديثة لجهاز الموجات الصوتية للقلب من شهر أغسطس 2009 إلى يناير 2012 لفحص 103 مريض يعانون من مرض فشل القلب المزمن في مركز جامعة كيانغسان ماليزيا الطبي لتقييم وظيفة القلب الانقباضية الطولية والتزامن الميكانيكي داخل البطين وتم قياس تركيز NT-proBNP في نفس الوقت. **النتائج:** تسارع القلب الطولي , تسارع القلب الجزئي, الإزاحة و التزامن الميكانيكي داخل البطين بالاعتماد على الانحراف المعياري (SD) من الوقت إلى ذروة سرعة الضغط الانقباضي (Tsr-SD) والإزاحة وتأخر انقباض الحاجز الأمامي للخلفي (AS-P) ارتبطت بأحداث فشل القلب. بالاعتماد على التحليل متعدد للمتغيرات تنبأت عوامل NT-proBNP و AS -P بشكل مستقل بأحداث فشل القلب ووجد ارتباط ملموس بين NT-proBNP, تسارع القلب الطولي ,الإزاحة, معدل الضغط الانقباضي و تسارع القلب الجزئي. لوغاريثمNT-proBNP ارتبطت بشكل معتدل مع الانحراف المعياري (SD) من الوقت إلى ذروة الإزاحة وذروة الضغط الانقباضي وارتبطت بشكل بسيط مع الفروق القصوى و (SD) من الوقت إلى ذروة سرعة الضغط الانقباضي وبالاعتماد على التحليل متعدد للمتغيرات و جد أن تركيز NT-proBNP إرتبطت بشكل ملموس بسن المريض و تسارع القلب الجزئي. **الخلاصة:** تقنية متابعة التنقيط بالموجات الصوتية للقلب طريقة واعدة لتسريع التطبيق السريري لتقدير حجم وظيفة عضلة القلب و التزامن الميكانيكي داخل البطين. وهذه التقنية مع زيادة تركيز NT-proBNP لديها المقدرة على تحديد المرضى الأكثر عرضة للوفاه والحاجة للترقيد في المستشفى.

مفتاح الكلمات: فشل القلب , تخطيط صدى القلب , اختلال البطين الأيسر , الناتيروتك ببتايد

ABSTRACT: ***Objectives:*** The aim of this study was to assess longitudinal systolic function and mechanical synchrony parameters derived from advanced speckle tracking echocardiography (STE) and to determine their correlation with N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Their influence on heart failure (HF) outcomes at a one-year follow-up, not clarified in previous studies, was also examined. ***Methods***: Advanced STE was performed from August 2009 to January 2012 in 103 chronic HF patients at the University Kebangsaan Malaysia Medical Center to assess their longitudinal systolic function and synchrony parameters; NT-proBNP blood measurement was taken at the same time. ***Results***: Longitudinal cardiac velocity; strain; strain rate; displacement; intraventricular mechanical dyssynchrony based on the standard deviation (SD) of time to peak systolic strain rate (Tsr-SD); displacement, and antero-septal to posterior (AS-P) delay were associated with cardiac events. In multivariate analysis, NT-proBNP and AS-P delay were identified as independent predictors for cardiac events. Significant correlations were found between NT-proBNP and longitudinal velocity; displacement; strain; strain rate, and ejection fraction. Log NT-proBNP levels correlated moderately with the SD of time to peak displacement and to peak strain, and there was a small correlation with maximal differences and SD of time to peak velocity. A multiple linear analysis revealed that NT-proBNP levels significantly correlated to age, ejection fraction and velocity. ***Conclusion***: Advanced STE is a promising technique which accelerates the clinical application of the quantification of myocardial function and synchrony. STE parameters and NT-proBNP have the ability to identify patients at higher risk of death and hospitalisation.

Keywords: Heart Failure; Echocardiography; Left Ventricular Dysfunction; N-terminal pro-BNP.

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Advances in Knowledge

- *This is the first study of its kind in Malaysia and the Middle East that uses multiple parameters derived from the advanced two-dimensional strain tool speckle tracking echocardiography (STE) supplemented by N-terminal prohormone of brain natriuretic peptide to predict cardiac events.*
- *STE is breaking new ground in heart failure (HF) monitoring and therapy so that treatment can be administrated earlier to high-risk patients as part of a HF management programme.*

Application to Patient Care:

- *HF management programmes have been developed to reduce the frequency and severity of these clinical events, but their effectiveness may be limited by physicians' difficulty in identifying patients at imminent risk.*
- *Reliable prediction may afford physicians the opportunity to intervene aggressively, potentially minimising the need for hospitalisation or the risk of a serious adverse outcome.*
- *The study emphasises the importance of promoting and improving cardiac services to HF patients.*

Heart failure (HF) constitutes a major world health problem. Despite therapeutic progress, the prognosis for patients with HF remains poor.[1,2] One possibility to improve HF management would be early detection and treatment of left ventricular (LV) dysfunction, which has traditionally been evaluated as left ventricular ejection fraction (LVEF) and LV end-systolic volume, both regarded as the simplest and most widely used parameters for global assessment of LV function.[3] Recently, new echocardiographic techniques have been introduced to evaluate myocardial mechanics. Tissue Doppler imaging (TDI) and two-dimensional (2D) speckle tracking echocardiography (STE) allow more objective quantification of myocardial mechanics in the form of tissue velocities, displacement, strain, strain rate and mechanical dyssynchrony assessment.

The TDI technique is limited by angle-dependency such that only deformation along the ultrasound beam can be derived from velocities while the *myocardium* deforms simultaneously in three dimensions. STE is a more recent technique that provides a global approach to LV myocardial mechanics, giving information about the three spatial dimensions of cardiac deformation. Systolic asynchrony is a relatively common finding in patients with systolic HF and is believed to indicate a more severe form of HF which is prognostically independent of QRS duration.[4–9]

Although systolic asynchrony often exists in patients with systolic HF who commonly have wide QRS complexes, recent studies observed that it also exists in about 30–40% of patients with a normal QRS duration and is related to increased morbidity and mortality.[4–8,10] In addition, the correction of dyssynchrony has been shown to improve the immediate haemodynamic effects, symptoms of HF, quality of life, exercise tolerance and survival in patients with chronic heart failure (CHF).[11–14] CHF is currently recognised as a clinical syndrome occurring not only as a result of mechanical dysfunction of the ventricles, but also due to complex molecular, endocrine, neuro-endocrine and inflammatory changes.[15] Neurohormonal activation plays a fundamental role in the onset and progression of HF, and the use of biochemical markers as prognostic indicators of HF have expanded in the last decade. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been studied as a biomarker of severity and prognosis of CHF in small studies and has shown to be very reliable.[16–19] The level of NT-proBNP remained predictive of death and of the combined endpoint of death and hospitalisation.

We performed this study to assess the prognostic value of multiple parameters of longitudinal systolic function and intraventricular synchrony derived from STE, also considering NT-proBNP levels for predicting adverse cardiac events in patients with CHF and examined the utility of NT-proBNP levels compared to multiple 2D-strain tool STE parameters.

Methods

The study enrolled 150 CHF patients who presented to the Cardiology Unit of the University Kebangsaan Malaysia (UKM) Medical Center between August 2009 and January 2012 with signs and symptoms matching the European Society of Cardiology Clinical Practice Guidelines for Heart Failure.[2]

Patients of either gender were recruited according to the following inclusion criteria: ≥20 years old, and CHF documented in medical notes. All patients gave written informed consent to take part in the study. Patients with severe renal failure (serum creatinine >5 mg/dl), no sinus rhythm, myocardial infarction within the previous 3 months, HF caused by *cor pulmonale*, congenital heart disease, constrictive pericarditis, hypertrophic or restrictive cardiomyopathy, or ventricular thrombus were excluded. Among the 150 patients initially enrolled in the study, 47 were disqualified, leaving 103 patients eligible for analysis. The study was approved by the Local Ethics Committee of UKM.

During the health examination, hypertension (HT) was defined by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication. Diabetes mellitus (DM) was defined by a plasma glucose concentration ≥11.1 mmol/L, the use of insulin or other anti-diabetic medicine, self-reported disease or haemoglobin A_{1c} levels ≥6.5%. Coronary artery disease (CAD) was defined by a history of hospital admission for acute coronary artery syndrome, percutaneous coronary intervention or coronary artery bypass grafting or major ischaemic alterations. LV systolic dysfunction was defined by a LVEF <50%. Primary endpoints included death or hospitalisation due to the deterioration of HF.

Hospitalisation for HF was defined as unplanned intravenous treatment of new or worsening HF with inotropic agents, diuretics, or vasodilators requiring an overnight stay in or admission to any healthcare facility. Cardiovascular death was defined as sudden cardiac death, or death attributed to HF, a cardiovascular procedure or another cardiovascular cause.

All patients were followed-up at the end of 12 months for the occurrence of HF-adverse cardiac events, which was prospectively defined as death, hospitalisation or an outpatient visit for worsening HF that required intensification of treatment.

At the time of echocardiographic examination, a blood sample was collected into tubes containing separating gel, processed, and frozen at -80 °C for later measurement of NT-proBNP using the cobas e 411 analyzer (Roche Diagnostics, Pleasanton, California, USA).

Baseline echocardiographic studies were performed in the left lateral *decubitus* position using a Vingmed Vivid i ultrasound machine (General Electric Healthcare, Fairfield, Connecticut, USA). Data acquisition was performed with a 3S transducer and apical views were obtained during breath hold and stored in a cineloop format from 6 consecutive beats. The LV eject was assessed by the biplane Simpson's rule.[20,21]

For STE analysis, tissue velocity imaging (TVI) 2D images were acquired in apical 2-, 3- and 4-chamber views. All of the images were recorded with a frame rate of ≥50 frames per sec (fps) to allow for the reliable operation of the software with the use of Vivid E9/EchoPAC for PC, Version 110 software (General Electric, Fairfield, Connecticut, USA).

From an end-systolic single frame, a region of interest was traced on the endocardial cavity; an automated tracking algorithm followed the *endocardium* throughout the cardiac cycle. Further adjustment of the region of interest was performed to ensure that all of the myocardial regions were included. The so-called 'speckles' which were equally distributed in the region of interest could then be followed throughout the entire cardiac cycle. The distance between the speckles was measured as a function of time, and parameters of LV function and myocardial deformation could be calculated. Finally, the *myocardium* was divided into 6 segments that were colour-coded as previously described and displayed into 6 segmental times to peak longitudinal systolic velocity, displacement, strain and strain rate curves.[22]

For longitudinal analysis, two different parameters for dyssynchrony were obtained: the maximal time delay between two segments in the septum and lateral, antero-septal and posterior walls of the LV. The basal and mid segments, were subjected to the measurement for longitudinal velocity, strain, strain-rate and displacement. Apical segments were prospectively excluded because of the relatively low velocity movement of the LV apex. The asynchrony index of the LV was also calculated through the standard deviation (SD) of time-to-peak systolic velocity (Tv-SD), strain (Tst-SD), strain-rate (Tsr-SD) and displacement (Td-SD), for 12 LV segments.[20,23,24]

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, strain, strain rate

and displacement. These were measured during the ejection phase, and the SD between all 12 segments was used as a measure of dyssynchrony.[25,26]

Data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 20 (IBM, Corp., Chicago, Illinois, USA). Categorical data were expressed as numbers and percentages, and compared with the Chi-square test. Data were tested for normality. Parametric data were expressed as mean ± SD and compared using the two-tailed Student's t-test. Non-parametric data were reported as median and at 25th and 75th percentiles and compared by the Mann-Whitney U test. Log-transformation and square were used to achieve normality in distribution.

Univariable simple linear regression analysis was used to determine the correlation between echocardiographic parameters and age as independent variables with log NT-proBNP levels as a dependent variable.

A multivariable linear regression analysis model was used to determine correlations between variables. A logistic regression analysis model was used to determine independent predictors of primary end points at the end of one year. A receiver-operating characteristic (ROC) curve was performed to calculate the optimal cut-off values with its sensitivity and specificity for predicting the primary endpoints. A *P* value of <0.05 was considered statistically significant.

Results

The mean age of the 103 patients in the study (n = 18 female; n = 85 male was 59 ± 10.6 years (range 31–81 years). Of these patients, 70 (68%) were hypertensive, 44 (42.7%) were diabetic, 81 (78.6%) had a history of CAD and 74 (71.8%) had dyslipidemia. The mean LVEF was 37.86 ± 13.23. Baseline clinical data of the patients are summarised in Table 1. The median NT-proBNP level among the 103 patients with systolic and diastolic HF in this study was 711.70 pg/ml (range 5–17,100 pg/ml; inter-quartile range (IQR) = 189.91–2125 pg/ml).

Simple linear regression analysis was performed between log NT-proBNP levels as a dependent parameter and age and other independent parameters of cardiac function and LV intra-ventricular mechanical dyssynchrony indices derived from advanced STE. These are shown in Table 2.

Table 1: Baseline clinical and advanced speckle tracking echocardiography parameters of the study population

Clinical variables	**Study Sample (N = 103)** **n (%)**
Age in years	59 (± 10.60)
Male	85 (82.5)
Female	18 (17.5)
HT	70 (68)
DM	44 (42.7)
CAD	81(78.6)
Dyslipidemia	74 (71.8)
NT-proBNP level, median (pg/ml; IQR)	711.70 (189.91–212.5)
Echocardiographic variables	
LVEF (%)	37.86 (13.23)
Average systolic velocity (cm/s)	2.34 (1.36)
Average strain (%)	-9.19 (5.18)
Average strain rate (s-1)	-0.76 (0.27)
Average displacement (cm)	5.38 (3.37)
Tv-SD (mins)	71.37 (3.37)
Tv-diff (mins)	236.26 (69.61)
Tst-SD (mins)	64.93 (36.76)
Tstr-SD (mins)	80.51 (24.45)
Td-SD (mins)	54.85 (33.89)
S-L delay, mins (median/IQR)	71 (30–124)
As-P delay, mins (median/IQR)	69 (26–133)

Results are presented as mean (standard deviation) for normally distributed parameters and median with inter-quartile range (IQR) 25th and 75th percentiles for non-normally distributed parameters.

HT = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; IQR = inter-quartile range; LVEF = left ventricular ejection fraction; 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; As-P = antero-septal to posterior.

There was a strong, negative and highly significant correlation between EF and log NT-proBNP levels (R = -0.828, *P* <0.0001, R^2 = 0.65), which implies that 65% of NT-proBNP variations can be explained by EF. No correlation was found between age and log NT-proBNP levels. The correlation between the parameters derived from the STE average and log NT-proBNP levels were strong, negative and

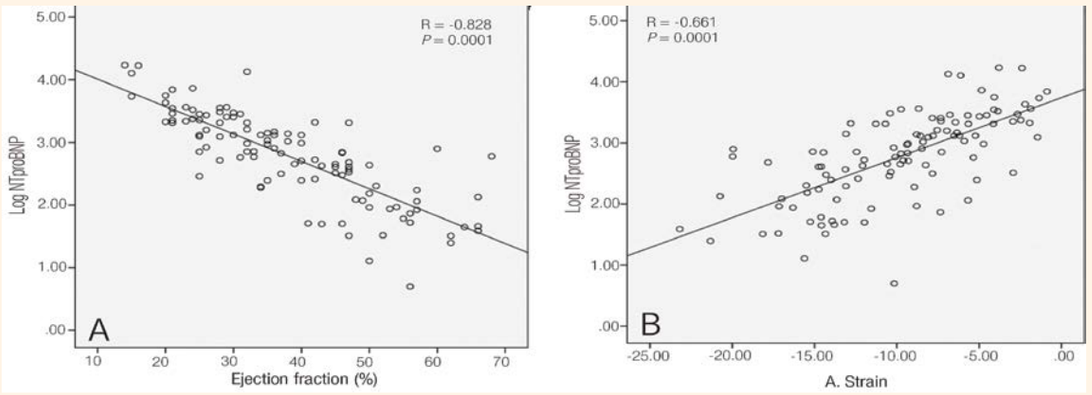

Figure 1 A & B. Scatter plots showing the correlation between log N-terminal prohormone of brain natriuretic peptide level and **A:** ejection fraction and **B:** longitudinal strain.

highly significant (R = -0.633, *P* <0.0001 and R = -0.625, *P* <0.0001, respectively). Additionally, R^2 = 0.400 and 0.391, which implies that 40% and 39% of NT-proBNP variations can be explained by the longitudinal velocity and displacement, respectively. There was also a strong and highly significant correlation between average and log NT-proBNP levels (R = 0.661, *P* <0.0001 and R = 0.623, *P* <0.0001, respectively, and R^2 = 0.437, 0.388). This implies that 43.7% and 38.8% of NT-proBNP variations can be explained by the longitudinal strain and strain rate, respectively. Additionally, log NT-proBNP levels correlated moderately but significantly with systolic dyssynchrony based on Tst-SD and Td-SD (R = 0.313, *P* <0.001 and R = 0.343, *P* <0.0001, respectively). There was also a small correlation with systolic dyssynchrony based on Tv-SD, Tsr-S and maximal time difference between 12 segments (Tv-diff) which was statistically significant (R = 0.243, *P* = 0.01 and R = 0.264, *P* <0.007, respectively) [Figure 1].

This study revealed that there was no relation between NT-proBNP levels and age, septal to lateral (S-L) delay, or AS-P delay. Analyses with a multiple linear regression model to confirm the important variables correlating with NT-proBNP, revealed that NT-proBNP levels were independently related to age, EF and longitudinal systolic velocity, and were significantly correlated to NT-pro BNP levels [Table 2]. Adjusted, these statistics can be expressed as R^2 = 0.72, *P* <0.0001, which implies that 72% of the variability in NT-proBNP levels can be explained by independent variables, and the EF was the strongest predictor of NT-proBNP levels (β = - 0.774, *P* <0.0001).

After 12 months, 35 of 103 patients (33.98%) had reached the primary endpoint; there were 22 (21.36%) hospitalisations for HF deterioration and 13 (12.62%) cardiac deaths. The significant characteristics of all patients are listed in Table 3. Patients with high baseline NT-proBNP levels were more prone to cardiac events than those with low NT-proBNP levels.

Table 2: Linear regressions in univariate and multivariate analyses correlation of log N-terminal prohormone of brain natriuretic peptide levels to age and advanced speckle tracking echocardiography parameters

	Univariate linear regression			**Multiple linear regression**	
	R	**R^2**	*P*	**β**	*P*
Age	-0.002	0	0.987	0.176	0.001
LVEF	-0.828	0.685	0.0001	- 0.774	0.0001
Strain	0.661	0.437	0.0001		
Strain rate	0.623	0.388	0.0001		
Displacement	-0.625	0.391	0.0001		
Average velocity	-0.633	0.4	0.0001	-0.141	0.045
S-L delay	0.011	0	0.913		
As-P delay	0.041	0.002	0.679		
Tv-SD	0.243	0.059	0.014		
Tv-diff	0.264	0.07	0.007	0.124	0.026
Tst-SD	0.313	0.098	0.001		
Tsr-SD	0.285	0.081	0.004		
Td-SD	0.343	0.118	0.0001		

Correlation is significant at < 0.05 level.

LVEF = left ventricular ejection fraction; S-L = septal to lateral; As-P = antero-septal to posterior; 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.

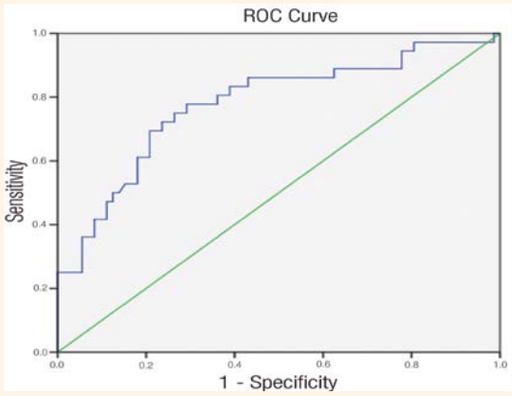

Figure 2. Receiver-operating characteristic curve analysis to determine the optimal cut-off value of N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) for prediction of cardiac events at the end of 12 months in 103 patients.

Parameters: NT-pro BNP; Cut-off: 948.5; Area under the curve: 0.780; Sensitivity: 74.3%; Specificity: 71%.

Multivariate logistic regression analysis demonstrated that independent predictors for cardiac events were NT-proBNP levels and AS-P delay (P <0.0001 and 0.049, respectively). The overall accuracy of this model to predict subjects prone to clinical events was 76.7% with 51.43% sensitivity and 89.70% specificity. Positive predictive value (PPV) was 72% and negative predictive value (NPV) was 78.2%.

In the receiver-operating characteristic curve (ROC) curve analysis, a 948.5 pg/ml NT-proBNP cut-off value revealed a sensitivity of 74.3% and specificity of 71% for the prediction of cardiac events. The area under the ROC in predicting cardiac events was found to be 0.780 (95% CI, 0.681–0.880) for NT-proBNP [Figure 2].

The results of cardiac function and mechanical LV dyssynchrony indices assessed by STE are displayed in Table 3. Parameters were measured from 12 segments obtained from apical 4-, 2- and 3-chamber views and then averaged according to longitudinal velocity, strain, strain rate and displacement. There were significant differences (P 0.0001) in these parameters between the two groups of clinical events.

The LV intraventricular delay, as measured by the SD of 12 segments derived from the 2D strain tool STE through measurement of Tsr-SD: P 0.022; Td-SD: P 0.028 and the AS-P delay (P 0.035) were prolonged and provided significant differences between the two groups of clinical events. However, the LV intraventricular delay (as measured by the SD of a 12-segment Tst-SD, Tv-SD, maximal Tv-diff between 12 segments and S-L delay) were prolonged

Table 3: Clinical and advanced speckle tracking echocardiography parameters between two groups of cardiac events

	Clinical Events		
	No	Yes	
	n = 68	n = 35	*P* value
Clinical variables			
Age in years	59 (11)	57 (9)	0.352
Female gender, n (%)	13 (19)	5 (14)	
Male gender, n (%)	55 (81)	30 (85.7)	0.541
CAD, n (%)	52 (76.5)	29 (83)	0.454
DM, n (%)	27 (39.7)	17 (48.6)	0.389
HT, n (%)	47 (69)	23 (65.7)	0.726
Dyslipidemia, n (%)	48 (70.6)	26 (74.3)	0.693
NT-proBNP, n (IQR)	428 (118.9–1195.5)	2125 (936–4307)	0.0001
Echocardiographic variables			n (%)
LVEF, mean (SD)	42 (12)	29.8 (11)	0.0001
Average velocity in cm/sec, mean (SD)	2.7 (1)	1.5 (1)	0.0001
Average strain, mean (SD)	-10.42 (5)	-6.8 (4.8)	0.0001
Average strain rate s^{-1}, mean (SD)	-0.82 (28)	- 0.6 (0.23)	0.001
Average displacement in cm, mean (SD)	6.2 (3.4)	3.79 (2.81)	0.001
Tv-SD in mins, mean (SD)	71.7 (23.3)	79.50 (26.7)	0.147
Tv-diff in mins, mean (SD)	228 (65.7)	252.40 (75)	0.108
Tst-SD in mins, mean (SD)	61.54 (36.6)	71.50 (36.7)	0.196
Tstr-SD in mins, mean (SD)	76.6 (23.7)	88.3 (21.5)	0.022
Td-SD in mins, median (IQR)	50.13 (33.3)	64 (33.6)	0.028
S-L delay in mins, median (IQR)	74 (30–130)	86 (30–160)	0.126
As-P delay in mins, median (IQR)	49 (21–100)	110 (47–181)	0.035

CAD = coronary artery disease; DM = Diabetes mellitus; HT = Hypertension; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; LVEF = left ventricular ejection fraction; SD = standard deviation; 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; As-P = antero-septal to posterior.

and statistically provided no significant differences between the two groups of clinical events. Clinical and echocardiographic data for the two groups are summarised in Table 3.

Clinical and echocardiographic parameters were investigated for their predictive value for clinical events by bivariate and multivariate analyses. In bivariate analysis, there was a higher prevalence of CAD (83%) and dyslipidemia (75%) among patients who developed cardiac events. On the other hand, HT (66.7%) and DM (50%) were less prevalent in this group. However, the *P* value was not significant. Longitudinal cardiac function, average EF, NT-proBNP and intra-ventricular mechanical dyssynchrony were significantly associated with the development of clinical events [Table 3].

NT-proBNP and AS-P delay were identified as the independent predictors of cardiac events (*P* 0.0001 and 0.035, respectively). The overall accuracy of this model to predict subjects having clinical events was 76.7% with 51.4% sensitivity and 89.7% specificity. The positive predictive value was 72% and the negative predictive value 78.2%.

We constructed the ROC curve to determine the optimal, average strain, average strain rate, Tsr-SD and AS-P delay cut-off value for predicting clinical events.

Discussion

STE is a novel method of quantifying global and regional cardiac longitudinal function from routine B-mode grey-scale images.[27,28] Tracking patterns of speckles quantifies tissue deformation without the directionality constraints of Doppler techniques. Image degradation and through-plane motion both compromise STE. Temporal resolution is lower than that obtained through TDI techniques. Conventionally, defining the region of interest remains user-dependent. The endocardial and epicardial borders are manually traced and fine-tuned to include all segments throughout the cardiac cycle.[27,28] Further adjustment is undertaken to optimise the tracking stability score.[27]

In this study, the more advanced 2D-strain tool was applied by using TVI scans in which the 2D-strain tool optimally combines TVI for a more comprehensive analysis and increased sensitivity. It has a built-in quality assurance that automatically evaluates the reliability of the results by looking at the variability of velocities in small tissue areas. It then chooses which acoustic markers to track, making the tool more robust than traditional STE.

This is the first study of its kind in Malaysia and the Middle East that uses multiple parameters derived from the advanced STE and biomarkers to predict cardiac outcome of patients with CHF by determining LV dysfunction and intraventricular dyssynchrony parameters. Considering the high worldwide cardiac death rate, we need to identify high-risk patients to reduce morbidity and mortality.

In this study, there was a higher prevalence of CAD (83%) and dyslipidemia (74.3%) among patients who developed cardiac events. On the other hand, HT (65.7%) and DM (48.6%) were less prevalent but not significant. There were significant correlations between NT-proBNP and some echocardiographic parameters; on the other hand, there was a correlation with advanced clinical cardiac outcome. Our findings are in accordance with other studies which showed that NT-proBNP levels are important in predicting cardiac events in HF patients.

This study emphasised that some echocardiography parameters and NT-proBNP levels provide a powerful incremental assessment of LV function and the prediction of adverse cardiac outcome. Elevated NT-proBNP levels correlated with several important echocardiographic parameters of systolic and diastolic HF.

The clinical applications of STE-derived myocardial velocity, displacement, strain and strain rate measurements are very promising for the assessment of LV function and the prediction of cardiac events at one-year follow-up; however, further refinement is required. Advanced STE has an advantage of ease of application and analysis.

Numerous echocardiographic techniques have been proposed for the assessment of LV function and intraventricular dyssynchrony, and echocardiographic dyssynchrony has been the subject of numerous publications. The currently observed differences between the results provided by different echocardiographic modalities is not entirely surprising since the methods represent independent approaches to the assessment of LV function and dyssynchrony. The lack of standardisation of imaging planes and different speckle tracking algorithms among vendors make comparisons or the establishment of normal values

with high levels of confidence difficult.

The recently published PROSPECT trial tested 12 different techniques to describe dyssynchrony and concluded that no single technique can be recommended as a standard.[29] Echocardiographic parameters have largely been studied in small, non-randomised studies with surrogate endpoints. However, PROSPECT identified that, outside of expert centres, reduced test reproducibility and marked intra-observer variability limited the clinical utility of many echocardiographic techniques.[29,30] In particular, the automated processing algorithm reduces the impact of operator skill and improves reproducibility while reducing analysis time.

The most recent expert consensus reported that there is a lack of scientifically verified data and all the statements and recommendations are primarily based on the opinions of experts and cannot provide an evidence base for potential clinical applications of this technique in multiple clinical scenarios. They therefore concluded that this methodology is not yet ready for routine clinical use.[31]

The present study demonstrates that evaluation of LV function and intra-ventricular dyssynchrony using advanced 2D strain tool speckle tracking analysis is feasible and predicts the cardiac outcome in heart failure patients. No data exist on this advanced 2D strain tool as a comprehensive tool.

The implications of these research findings are ground-breaking in HF monitoring and therapy, allowing earlier treatment and HF management to be administrated to high-risk patients. This study emphasises the importance of promoting and improving cardiac services to HF patients.

The limitations of this technique include the significant time required for post-processing; differences among vendors, driven by the fact that STE analysis is performed on data stored in a proprietary scan line format which cannot be analysed by other vendors' software; limited experience in cross-comparing data from different vendors' images, and the need for further investigation.

All echocardiography measurements in this study were obtained by a single cardiologist without intra- or inter-observer variability. This study did not compare circumferential or radial fibres function with longitudinal fibres function.

Conclusion

The advanced 2D-strain tool STE is a promising technique which is accelerating the clinical application of the quantification of myocardial velocity and deformation. One important advantage is based on its TVI and grey-scale images, with their comprehensive analyses which are independent of angle of incidence and less dependent on image quality, making it the most robust technique. STE is a reliable and feasible tool for evaluating longitudinal myocardial function and synchrony, and also allows the further identification of patients at higher risk of death and hospitalisation. It appears more trustworthy than conventional STE and TDI; however, further studies need to be done before it is implemented widely in clinical practice.

References

1. Cleland JG, Swedberg K, Follath F. The EuroHeart Failure Survey programme: A survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J 2003; 24:442–63.
2. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, et al. Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26:1115–40.
3. Edvardsen T, Helle-Valle T, Smiseth O. Systolic dysfunction in heart failure with normal ejection fraction: Speckle-tracking echocardiography. Prog Cardiov Diseases 2006; 49:207–14.
4. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003; 89:54–60.
5. Ghio S, Constantin C, Klersy C, Serio A, Fontana A, Campana C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004; 25:571–8.
6. Bleeker GB, Schali J, Martin J, Molhoek SG, Verwey HF, Holman ER, et al. Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2004; 15:544–9.
7. Sade LE, Kanzaki H, Severyn D, Dohi K, Gorcsan J, III. Quantification of radial mechanical dyssynchrony in patients with left bundle branch block and idiopathic dilated cardiomyopathy without conduction delay by tissue displacement imaging. Am J Cardiol 2004; 94:514–18.
8. Bader H, Garrigue S, Lafitte S, Reuter S, Jais

P, Haissaguerre M, et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol 2004; 43:248–56.

9. Cho GY, Song JK, Park WJ, Han SW, Choi SH, Doo YC, et al. 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; 46:2237–43.
10. Fauchier L, Marie O, Casset-Senon D, Babuty D, Cosnay P, Fauchier JP. Interventricular and intraventricular dyssynchrony in idiopathic dilated cardiomyopathy. J Am Coll Cardiol 2002; 40:2022–30.
11. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 24:1845–53.
12. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350:2140–50.
13. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–49.
14. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105:438–45.
15. Buunwald E, Bristow MR. Congestive heart failure: Fifty years of progress. Circulation 2000; 102:IV14–23.
16. Hartmann F, Packer M, Coats AJS, Fowler MB, Krum H, Mohacsi P, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic conges¬tive heart failure: A substudy of the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) trial. Circulation 2004; 110:1780–6.
17. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-Terminal pro-brain natriuretic peptide: A new gold standard in predicting mortality in patients with advanced heart failure. Eur Heart Fail 2003; 24:1735–43.
18. Song BG, Jeon ES, Kim YH, Kang MK, Doh JH, Kim PH, et al. Correlation between levels of pro-B- type natriuretic peptide and degrees of heart failure. Korean J Inter Med 2005; 20:26–32.
19. Weber T, Auer J, Eber B. The diagnostic and prognostic value of brain natriuretic peptide and aminoterminal (nt)-pro brain natriuretic peptide. Curr Pharm Des 2005; 11:511–25.
20. Gorcsan J, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. Am J Cardiol 2004; 93:1178–81.
21. Dohi K, Suffoletto MS, Schwartzman D, Ganz L, Pinsky MR, Gorcsan, J. Utility of echocardiographic radial strain imaging to quantify left ventricular dyssynchrony and predict acute response to cardiac resynchronization therapy. Am J Cardiol 2005; 96:112–16.
22. Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography—From technical considerations to clinical applications. J Am Soc Echocardiogr 2007; 20:234–43.
23. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105:438–45.
24. Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. 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.
25. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, et al. 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; 110:66–73.
26. Yu CM, Bax JJ, Gorcsan J. Critical appraisal of methods to assess mechanical dyssynchrony. Curr Opin Cardiol 2009; 24:18–28.
27. Gorcsan J, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007; 50:1476–83.
28. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006; 113:960–8.
29. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008; 117:2608–16.
30. Bax JJ, Gorcsan J III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: Results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. J Am Coll Cardiol 2009; 53:1933–43.
31. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for quantitative evaluation of cardiac mechanics: ASE/EAE Consensus Statement on Methodology and Indications: Endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011; 24:277–313.