Relation between global longitudinal strain and serum natriuretic peptide levels in acute heart failure

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Introduction:

Heart failure is a major public health problem with a prevalence of more than 23million worldwide and a survival estimates about, 50% and 10%, at, 5 and 10, years.[(1)] To improve its grave prognosis, early identification of cardiac dysfunction is mandatory. [(2)]

The routinely used echocardiographic parameter (LVEF) is not sensitive enough to detect myocardial dysfunction, [(3)]as it is mainly quantify overall volume displacement without detailed information on myocardial function. [(4)]

The myocardium have complex anatomy consist of subendocardial longitudinally oriented fibers, mid-wall circumferentially oriented fibers and subepicardial obliquely oriented fibers.[(4)]

The longitudinal fibers are very sensitive to wall stress, and can show abnormal contractile features even in the context of an apparently normal left ventricular ejection fraction (LVEF). [(5)]

Therefore, we suggest that measuring the longitudinal fiber shortening may help in early identification of cardiac dysfunction.

Two dimensional speckle tracking allows the quantification of systolic longitudinal fiber shortening, which may expressed as regional and global longitudinal strain (GLS). [(6)]

Brain natriuretic peptide and NT-proBNP levels, which is recommended in allpatients with acute dyspnea and suspected AHF according to current ESC guidelines,[(7)] are increased in HF and correlate well with ventricular wall stress and severity of HF. [(8)]

Therefore, some authors hypothesized that impaired GLS should be associated with high serum NT-proBNP. [(9)]

Aim of the work:

To evaluate if the correlation between GLS and BNP is more significant than the correlation between LVEF and BNP in patients with acute heart failure.

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Patients and method:

Study design and population:

We conducted a prospective study of patients who were admitted to CCU in Aswan university hospital with acute heart failure from March 2016 to September 2016.All patients provided a written consent before enrollment to the study. Patients withnon-sinus rhythm, chronic chest disease, renal impairment (eGFR<60), anemia (HB<9), insufficient image quality or inability to provide written consent were excluded from the study.

The patients were prospectively classified according to Framingham criteria [(10)]in the ER then they were admitted to CCU and managed according to current ESC heart failure guidelines. Patients' data including full history, clinical examination, clinical events during follow up and medical treatment were registered in the hospital records.

Blood sampling and NT-proBNP determination:

Blood sampling procedures and assay of NT-proBNP from peripheralsamples of plasma were gotten after written informedconsent within 24 h of admission.Analysis of NT-proBNP was executed using NT-proBNP ELISA kits (KA 3099, Abnova©) immediately after blood sampling.In addition, routine biochemical work-up was performed including creatinine, hemoglobin, LDL, cholesterol, glycatedhemoglobin (HbA1C), sodium, potassium and cardiac enzymes during the hospital stay. Estimated glomerular filtration rate (eGFR) was measured using Cockcroft-Gault formula. [(11)]

Echocardiography:

Echocardiographic examination was performed by using Philips IE 33© machine with simultaneous ECG tracing within 24 hours from admission.Images were obtained at a frame rate of 60–75/s for three consecutive cycles andanalysis was performed by QLAP 9 on the machine by a single experiencedoperator blinded to clinical and biochemical information.Two-dimensionalspeckle tracking was executed by means of a semiautomaticalgorithm. In short, using manual identification,three reference points (two annular and one apical) were selectedin each of the three apical views, to enable the softwareto monitor the myocardium in a semi-automated mannerin the course of the cardiac cycle. Each ventricular wall wassubsequently subdivided into three segments to realizethe creation of 17 segments covering the whole myocardium.Accurate manual inspection for tracking purposes was performed,and in the case of unsatisfactory tracking, thesegmentwould have been ousted from the analysis and if more thanthree segments have been ousted, the case excluded from the study.

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Longitudinal straincurves were built for each segment and the maximum valuewas determined. The GLS was then computed as the averageof all 17 segments.LVEF was obtained according to modified Simpson's method.

Statistical analysis:

All statistical tests were performed with a statistical analysis program (SPSS 15.0 for Windows). The distribution of the data was assessed using the one-sample D'Agostino-Pearson test. Continuous variables displaying normal distribution were expressed as mean ± SD, while values withasymmetric distribution were expressed as medians with interquartile ranges. Categorical variables were presented as percentage (%). A general linear regression model was built by including into it both continuous and categorical variables.NT-proBNP was logarithmically converted (log10) to make the variance as stable as possible according to the assumptions of multiple regression. A P-value < 0.05 was regarded significant. All relevant variables were entered and a parsimonious model was realized by subsequent variable elimination in a backward stepwise manner using P < 0.1 as a retention criterion. Values of NT-proBNP above the median (50th percentile) were compared with those located below the median (lower quartiles) and separate logistic regression models were set up for GLS and LVEF as a single predictor variable. Comparison of each method's predictive potential was performed by comparing the C-statistic derived from the area under the receiveroperating characteristic (ROC) curves

Results:

The total study population consisted of 139 patients that were diagnosed as AHF in the ER. Twenty-three (23) patients were excluded due to atrial fibrillation,12 were excluded due to chronic chest disease, 8 due to renal impairment, 5 due to anemia and 3 due to poor image quality. Thus, 88 patients were included in the studywith mean age (53.1±9.8) range from 25 to 70 years, 73.9% were males and 26.1% were females. Mean LVEF was 36.6% and mean LV GLS was-10.2%. The level of NT-proBNP ranged from 288 to 31,050pg/ mL, with a median of 2965 pg/mL and mean(6399.8±7912.8).

The overall linear relationships between log(NT-proBNP) with GLS and LVEF are shown in Figures 1,2.Correlation between log (NT-proBNP) and GLS was significant (P = 0.0001, r = 0.93) (Fig. 1). The observed correlationbetween log (NT-proBNP) and LVEF was also significant, butexplained a smaller magnitude of the variance (P = 0.001, r =-0.36) (Fig. 2).

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The patients were divided into three groups depending on their ejection fraction according to current ESC guidelines as follow;heart failure with reduced ejection fraction (HFREF) (56 patients, 63%), heart failure with mid-range ejection fraction (HFMrEF) (20 patients, 23%) and heart failure with preserved ejection fraction (HFpEF)(12 patients, 14%). Then, they were analyzed separately,log (NT-proBNP) exhibited a stronger overall correlationwith GLS (HFREF, P = 0.0001, r = 0.94; HFMrEF, P = 0.0001, r = 0.92; HFpEF, P = 0.0001, r = 0.95) compared with LVEF (HFREF, P = 0.0001, r = -0.47; HFMrEF, P = 0.01, r = -0.32; HFpEF, P = 0.2, r = -0.23).
In multiple linearregression analysis, GLS was shown to be as an independentpredictor of log (NT-proBNP), within a parsimonious modelincluding age,sex, body mass index, estimated glomerular filtrationrate, DM,ABP, and LVEF (rpartial = 0.7076; P < 0.001) (Table 1).
However, the C-statistics for GLS were significantlyhigher than for LVEF (AUC: 0.99(GLS) vs. 0.70 (LVEF); P= 0.001) (Fig. 3,4). In other words, the ability of GLS to predictthe association with a relatively high level of NT-proBNP,i.e., located above its 50th percentile, was compared with thatexhibited by LVEF. In this way, the value of GLS ≥ -10.4%was shown to have the best diagnostic accuracy (sensitivity= 100%; specificity = 87%) in predicting thepresence of relatively high (i.e., above the median) levels ofNT-proBNP, with an AUC of 0.99. Similarly, among all valuesof LVEF detected in the patient population, an LVEF ≤34.5% could achieve the best diagnostic accuracy (sensitivity =88%; specificity = 43 %) in the detectionof relatively high levels (i.e., above themedian) of NTproBNP, although showing an AUC of 0.70, namely,significantlylower than that exhibited by GLS (P = 0.001).

Discussion:

The main finding of this prospective study was that longitudinal function measured by GLS had a significantly strong correlation to the level of neurohormonal activation (r=0.93; P=0.0001) in patients with acute heart failure.
The observed correlation between log (NT-proBNP) and left ventricular ejection fraction (LVEF) was also significant, but explained a smaller magnitude of the variance (r = -0.36; P = 0.001).
In multiple linear regression analysis, GLS was shown to be the strongest independent predictor of log (NT-proBNP), within a parsimonious model including age, body mass index, estimated glomerular filtration rate, systolic

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blood pressure, diastolic blood pressure, DM and LVEF(β (regression coefficient) = 1451, rpartial = 0.77; P=0.001).

In subgroup analysis, we also demonstrated that GLS had significant correlation with NT-proBNP in patients with heart failure with preserved and mid-range ejection fraction as well as heart failure with reduced ejection fraction but LVEF was not correlated to NT-proBNP in patients with heart failure with preserved EF.

The C statistics for GLS were significantly higher than for LVEF (area under the curve (AUC): 0.99 (GLS) vs. 0.70 (LVEF). The observed relationship between GLS and NT-proBNP could reflect a pathophysiological connection between longitudinal fiber dysfunction and secretion of natriuretic peptides.

NT-proBNP is released from the myocardium when it is exposed to stretch and increased wall stress, [12] However it remains unknown whether LV GLS reflects e.g., myocardialwall stress, [13]fibrosis [14]or subclinical ischemia [15] in HF patients.

Iwanaga et al. [13] explored the relationship between wall stress'WS' and BNP in a cohort of 160 heart failure patients where a strong positive correlation was observed, and this was consistent when patients were divided according to systolic and diastolic heart failure. The relationship between longitudinal function and WS has not been explored in detail with invasive hemodynamics monitoring in humans; however, an animal study by Donal et al. clearly demonstrated that longitudinal function was more susceptible to increased WS whereas intact circumferential function served to preserve radial fractional shortening of the cavity diameter.[16]

Previous studies examined LV GLS and NP in chronic systolic HF, in a study of 137 patients with suspected HF Yoneyama et al. [17] observed that plasma concentrations of brain-natriuretic-peptide (BNP) were correlated to functional class, decreased LVEF and an impaired GLS in patients with both systolic and diastolic dysfunction.

Nahum et al. [18] who examined 125 patients with chronic systolic heart failure found significant association between both GLS and NT-proBNP support this.

In addition,Renato De Vecchis et al. [19], who carried out a retrospective study that involved 118 patients with CHF found that GLS was more accurate compared with LVEF in predicting increased levels of NT-proBNP inpatients with preserved and reduced LVEF.

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F Gaborit et al. [20] found that Impaired LV GLS is associated with increased plasma concentrations of NP in 149 patients with verified systolic HF at the baseline visit in an outpatient HF clinic.

Other studies have evaluated the relationship between LV GLS and neurohormonal markers in other types of patients.

For example, Andrew Goodman et al. [21] Proved that BNP and LV GLS provide incremental (additive not duplicative) prognostic information over established predictors, suggesting that both play a synergistic role in defining outcomes in normal LVEF patients with significant aortic stenosis.

In patients with acute myocardial infarction, Ersbøll et al. observed that impaired LV GLS was correlated to plasma concentrations of NT-proBNP[22] and risk of HF during the admission. [23]

It should be noted that both LV GLS and natriuretic peptides may be indirect measures of myocardial wall stress so future studies should evaluate the relationship between wall stress based on invasive measures with LV GLS, and plasma concentrations of NP's to confirm this hypothesis.

Study limitations:

- Lack of comparison with the TDI-derived indexes, both systolic and diastolic mitral annular velocities, which hindered us from using the E/e' in our analyses and comparisons.
- Lack of comparison with invasive hemodynamic method (End diastolic pressure) as the patients in our study are in acute stage and hemodynamic unstable.

Conclusion:

- LV GLS could provide a good predictive value of level of NT-proBNP independent on other varieties including age, sex, D.M, arterial blood pressure, GFR, BMI and LVEF.
- LV GLS was superior to the routinely used echocardiographic parameter, LVEF, in predicting the level of NT-proBNP in patients with acute heart failure.

Recommendations:

- We recommend the use of LV GLS in evaluation of patients with acute heart failure.
- We recommend studying the relation between LV GLS and wall stress with invasive hemodynamic method.

Figures and tables

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Figures:

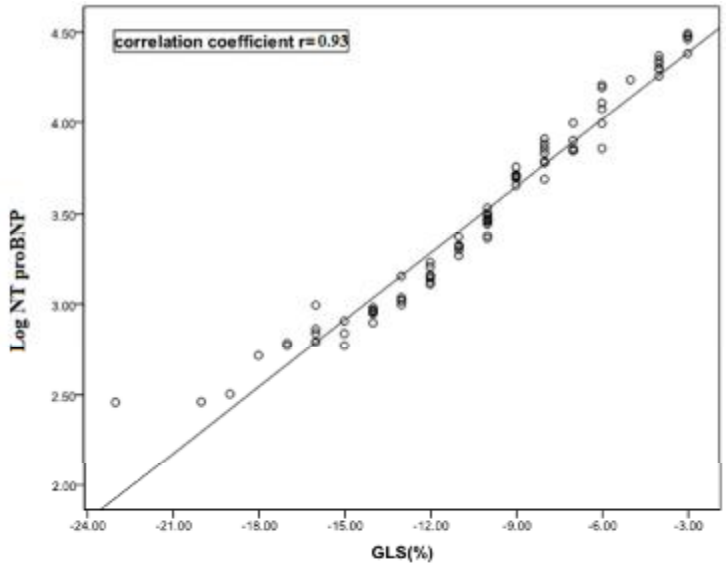

***Figure 1*:** Linear regression model for correlation between NT-proBNP and GLS.

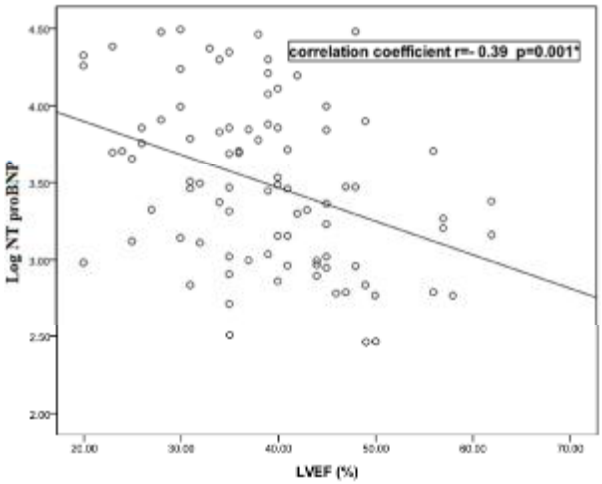

***Figure 2*:** Linear regression model for correlation between NT-proBNP and LVEF.

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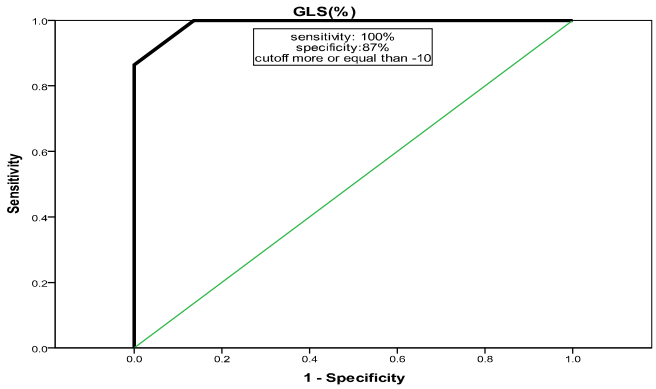

***Figure 3*:** ROC curve analysis representation of the diagnostic performance (AUC = 0.99) of GLS as a predictor of relatively high values of NT proBNP.

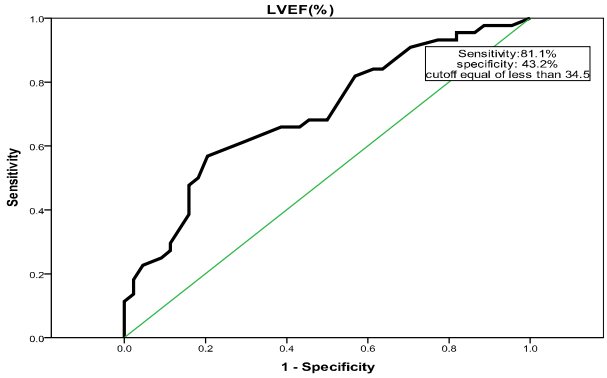

***Figure 4*:** ROC curve analysis representation of the diagnostic performance (AUC = 0.70) of LVEF as a predictor of relatively high values of NT proBNP.

Tables:

Table 1: The Multiple Linear Regression Analysis Showed That GLS Is the Best Independent Predictor (rpartial = 0.78) of High Levels of NT-proBNP, Within a Parsimonious Model Including Age, Sex, BMI, eGFR, systolic blood pressure, diastolic blood pressure, D.M., and LVEF.

Dependant variable	NT-proBNP (pg/mL)				
R^2	0.67				
Adjusted R^2	0.65				
Independent variable	**Beta**	**Standard error**	**T**	**r partial**	**P**
SPB	-12.4	28.6	-0.43	-0.05	0.6
DPB	-15.9	45.6	-0.35	-0.04	0.7
GLS(%)	1438.5	134.6	10.6	0.78	0.001*
LVEF(%)	-32.4	67.3	-0.48	-0.03	0.6
Age	-41.3	65.2	-0.63	-0.05	0.5
BMI	-215.5	286.8	0.75	-0.05	0.4
Sex	-400.1	1249.1	-0.32	-0.02	0.7
DM	716.6	1076.6	0.66	0.04	0.5
GFR	-124.1	131.4	-0.94	-0.08	0.3

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