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# The value of left ventricular strain in predicting adverse outcomes after coronary artery bypass surgery

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## ABSTRACT

*Objective:* assess the validity of global LV strain and strain rate (SR) to conventional echo parameters and N-Terminal proBNP (Brain Natriuretic peptide) in patients with CAD (coronary artery disease). *Methods:* the study included patients with CAD and LVEF ≥ 45%, with or without mitral valve regurgitation. The study carried out during the period from December 2017 to March 2018. The patients were scheduled for CABG±MVR (mitral valve replacement). Longitudinal and circumferential LV strain and SR were measured in addition to conventional echo parameters. NT-ProBNP and LV End Diastolic Pressure (LVEDP) were additional parameters to evaluate cardiac function. All the measurements were performed within one week prior to surgery. *Results:* The incidence of early adverse outcome after surgery was 35.6%. The mean LV longitudinal strain was the single best parameter in predicting adverse outcome, while global LV circumferential strain and strain rate followed closely in validity. *Conclusion:* The mean LV longitudinal, circumferential strain & strain rate provides a valuable tool for selecting candidates for CABG±MVR assuring a plausible outcome after surgery.

**Keywords:** LV Strain, adverse surgical outcome, Coronary artery bypass graft, proBNP

## 1. INTRODUCTION

Coronary artery disease (CAD) is a major cause of mortality and morbidity in developed countries. Countries like Africa and the Middle East bear a heavy burden from cardiovascular disease. The prevalence of CAD is promoted in turn by a high prevalence of cardiovascular risk factors, particularly smoking, hypertension, dyslipidemia, diabetes, and sedentary lifestyles. In Egypt, the prevalence of CAD is 8.3%, Coronary death range from 12-17% (Almahmeed *et al.*, 2012). Coronary artery bypass graft (CABG) surgery is a primary treatment option when intervention cannot be done, usually in cases of multi vessel coronary artery disease, or even in single vessel disease. CABG can be life-saving, as the annual mortality rate is more than 4-fold greater in patients with a significant viable myocardium who were treated medically compared to those who underwent revascularization (Krittayaphong *et al.*, 2008).

Pro brain natriuretic peptide (proBNP) is a 108 amino-acid propeptide synthesized by myocyte, predominantly from the left ventricle, in response to the increased wall stretch & wall tension & its main biological effect are regulation of blood pressure, blood volume & salt balance. Serum NT-proBNP levels are associated with a higher postoperative early and mid-term mortality, as well as morbidity, in patients undergoing isolated CABG, a predictor for atrial fibrillation & arrhythmias post CABG, also it correlated with other echo parameter (Samy *et al.*, 2012).

The objective of the current work to assess echocardiographic predictors for coronary artery bypass surgery, using conventional echocardiographic parameters and global LV longitudinal strain, Global LV circumferential strain, Longitudinal LV strain rate, plus serum level of biomarker N. Terminal ProBNP (brain natriuretic peptide), LV end diastolic pressure-LVEDP- (measured by catheterization) to predict adverse cardiac surgery outcomes post CABG.

## 2. PATIENTS AND METHODS

***Study sample***

A prospective cohort study, the initial recruited sample was 144 patients, from this primary sample only 104 patients were scheduled for CABG±MVR after excluding 40 patients with LV systolic dysfunction (LVEF ≤ 35% or large scarred apical aneurysm).

***Study setting***

The study carried out in specialized cardiac center, during the period between December 2017 and March 2018. A comprehensive and analyzable preoperative evaluation using conventional and 2D strain echocardiography, coronary angiography, and N. Terminal ProBNP measurement.

***Ethical approval***

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Code: 2012/0124) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

***Informed consent***

Informed written consent was obtained from all individual participants included in the study.

***Conventional echo cardiograph***

Evaluation of LV function using conventional LVEF, the cursor was at the tips of mitral valve leaflets in Para sternal long axis view (if LVEF <55% indicate mild impaired, <45% considered moderately impaired, <35% considered severely impaired & was excluded from study). LV septal wall thickness was measured from the leading endocardial edge to leading epicardial edge. LV end diastolic septal wall thickness (value of ≥ 12mm considered to be hypertrophied). LV End systolic volume indexed (value >50ml considered mild systolic dysfunction. value >70ml considered to be significantly impaired).

***Two-dimensional speckle tracking analysis***

Using commercially available 2D strain software (IE 33 Philips). Acquisition of 3 parasternal views apical 2 chamber. 3 chamber & 4 chamber views all images taken at end expiration to avoid LV apical for shortening reducing sector width & depth was tools used to increase frame rate for better image resolution all images were digitally stored at a high frame rate (>69 frames/s, mean 74 ± 17). Region of interest was localized at LV endocardial border 2 at base one apical to include the entire myocardium at end systolic frame. The software algorithm automatically segmented the LV into six equidistant segments and selected suitable speckles in the myocardium for tracking. The software algorithm then tracked the speckle patterns on a frame-by-frame basis using the sum of absolute difference algorithm. Finally, the software automatically generated LV strain profiles for each of the six segments of each view, from which end-systolic strain was measured. The average value of strain at each level (basal, middle, and apical) and global strain obtained using Bull eye model measuring peak regional & global LV longitudinal circumferential & strain rate of 17 LV segments was calculated.

All measurements were preformed off-line on a dedicated workstation using commercially available 2D strain software (IE 33 Philips). The operator was blinded to patient's outcome (Coronary angio & N. terminal B.N.P level). Longitudinal, Circumferential & strain rate was computed using 2D-speckle-tracking analysis by automated function imaging (AFI). For strain processing, the peak of the R-wave on the electrocardiogram was used as the reference time point for end-diastole and segments with poor-quality tracking were manually discarded. GLS & circumferential strain & strain rate was only computed from patients with >87% of segments adequately tracked (≥15 segments for a 17-segment model). An average of (<-25%) for normal circumferential strain any value assessed by AFI was considered as impaired, an average of (<-1 $S^{-1}$) for strain rate any value assessed by AFI were considered impaired strain rate.

***Invasive hemodynamic measurement***

LV end diastolic pressure was calculated in all patient prior to LV angiography.

***Primary early adverse outcomes of surgery***

LV dysfunction (defined as LVEF less than 35%) occurred or persisted within a maximum period of 12 weeks after surgery, and death were the primary early adverse outcomes post-CABG in this study.

***Inclusion criteria***

Patients with CAD and LVEF ≥35%, with or without mitral valve regurgitation.

***Exclusion criteria***

Severe LV systolic dysfunction (LVEF ≤ 35% or large scarred apical aneurysm).

***Statistical analysis***

Two samples t test used to analyze the differences in means between two groups (if both follow normal distribution with no significant outlier), chi square test used to analyze the discrete variable .Receiver operator curve used to see the validity of different parameters in separating active cases from control (negative cases) and area under the curve i.e. AUC and its p value prescribe this validity (if AUC ≥ 0.9 mean excellent test, 0.8 – 0.89 means good test, 0.7 – 0.79 fair test otherwise unacceptable). SPSS 18.0.0 (Chicago, IL) software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05.

## 3. RESULTS

***Demographic data***

The results presented in this study were based on the analysis of 104 cases with CAD who were planned to undergo cardiac surgery. The age of study participants ranged between 34 and 78 years with a mean of 57 ±8.4 years. Males constituted a round two thirds of the studied sample (65.4%) (table 1).

**Table 1** demographic and clinical characteristics of the patients

| Variables | Value |
|---|---|
| **Age (years), mean ± SD** | 57±8.4 |
| **Age group, n (%)** | |
| **<50 years** | 18 (17.3%) |
| **50-64 years** | 62 (59.6%) |
| **65-80 years** | 24 (23.1%) |
| **Gender, n (%)** | |
| **Female** | 36 (34.6%) |
| **Male** | 68 (65.4%) |
| **Hypertension, n (%)** | 67 (64.4%) |
| **Diabetes mellitus, n (%)** | 45 (43.3%) |

***Incidence rate of adverse outcome***

Either death or dysfunctional heart (LV dysfunction with LVEF<35%) that may happen during or after cardiac surgery constituted what was termed as adverse outcomes. More than one third (35.6%) of studied patients developed an adverse outcomes during or after surgery. The incidence rate of adverse outcome in the reference population of IHD patients was 35.6 with 95%CI: 26.5 to 45.6%, while case-fatality rate for the surgical procedure was 4.8% of study sample with 95%CI: 1.6 to 10.9%.

***The difference in mean of selected parameters in the presence and absence of adverse outcome***

No obvious or statistically significant differences in mean age were observed between those developing an adverse outcome during or after surgery and those with uneventful recoveries. Age is therefore not expected to confound the prediction of echo measurements for adverse outcome. All echo cardiograph parameters and serum NT-proBNP show significant difference according to outcome of surgery (as illustrated in table 2).

**Table 2** The difference various variables in the study prior to surgery between subjects developing adverse outcomes (death or dysfunctional heart) after surgery and those with uneventful recovery

| | Adverse outcomes | | p-value |
|---|---|---|---|
| **Variables** | **Negative** | **Positive** | - |
| **Number** | **67** | **37** | - |
| **Age (years), mean ± SD** | 57.1 ±8.4 | 56.8 ±8.5 | 0.860 |
| **Serum NT-proBNP (pg/ml), mean ± SD** | 660.8 ±471.6 | 1560.3 ± 529.9 | <0.001 |
| **LVEDV indexed ($ml^3/m^2$), mean ± SD** | 41.3 ± 12.3 | 56.6 ± 15.9 | <0.001 |
| **LV End diastolic pressure (mmHg), mean ± SD** | 18.5 ± 4.5 | 26.1 ± 3.3 | <0.001 |
| **LV Wall thickness (mm), mean ± SD** | 14 ± 2.3 | 11.1 ± 1.8 | <0.001 |
| **MAPSE (mm), mean ± SD** | 13.5 ± 2.6 | 7.8 ± 1.5 | <0.001 |
| **LVEF (%), mean ± SD** | 59.7 ± 7.1 | 51.7 ± 8.6 | <0.001 |
| **Global LV longitudinal strain (-%), mean ± SD** | 19.6 ± 2.6 | 13.1 ± 2.8 | <0.001 |
| **Global longitudinal strain of LV parts, mean ± SD** | | | |
| **Basal (- %)** | 20 ± 4.8 | 13.6 ± 3.4 | <0.001 |
| **Mid (- %)** | 19.2 ± 3.9 | 12.9 ± 3.9 | <0.001 |
| **Apical (- %)** | 19.2 ± 3.9 | 12.9 ± 3.9 | <0.001 |
| **LV strain rate ($s^{-1}$), mean ± SD** | 2 ± 0.5 | 1.1 ± 0.4 | <0.001 |
| **Global LV circumferential strain (- %), mean ± SD** | 33.7 ± 4.6 | 19.2 ± 6.1 | <0.001 |

***ROC analysis and assessment of validity***

The mean LV longitudinal strain prior to surgery was an almost perfect test (ROC area = 0.99) in predicting the adverse outcomes. Another two LV strain measurements, namely circumferential and strain rate were also associated with an excellent test validity in predicting adverse outcome (ROC area = 0.96, 0.93 and 0.97 respectively). The 3 longitudinal LV strain (basal, mid and apical) in addition to LV End diastolic pressure, LV end diastolic wall thickness and serum NT-proBNP were associated with a good test validity (ROC area ≥ 0.85). The LV end systolic volume and EF were the least valid parameters evaluated as a fairly valid test (ROC area around 0.8), (as illustrated in table 3 and figure 1).

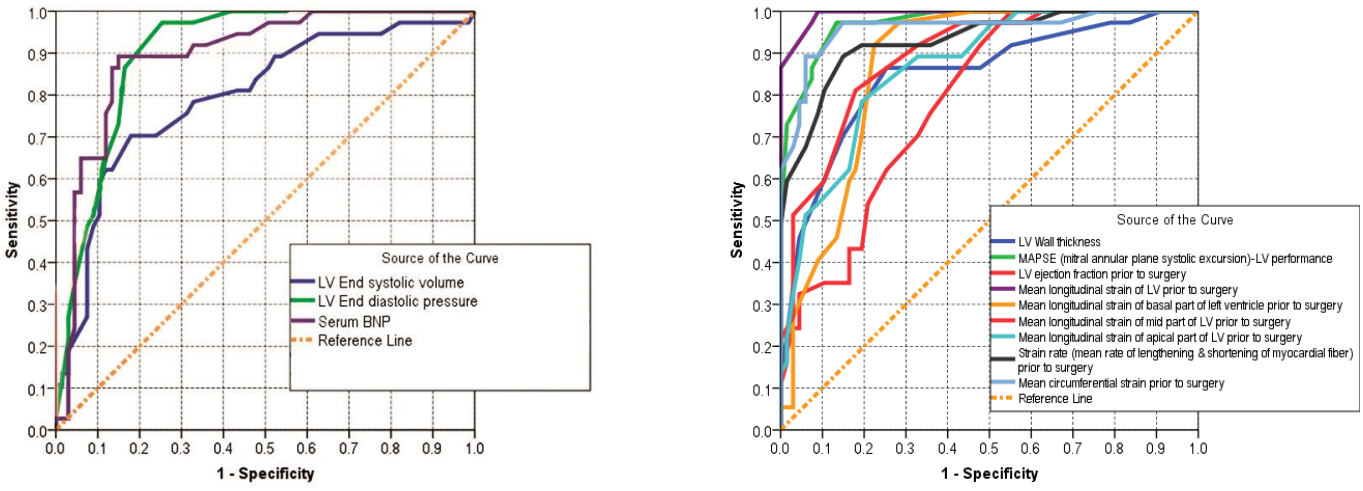


**Figure 1** ROC curve showing the trade-off between sensitivity (rate of true positive test results) and 1-specificity (rate of false positive test results) for selected measurements prior to surgery when used as tests to predict an adverse outcome of surgery. The figure in the *left* is for variables that predicts an outcome when larger in magnitude, while the figure in the *right* is reserved for variables that works in opposite direction predicting an outcome when smaller in magnitude.

**Table 3** ROC area for selected measurements prior to surgery when used as tests to predict an adverse outcomes of surgery (Death or Dysfunctional heart)

| Adverse outcome of surgery | AUROCC | P-value |
|---|---|---|
| **Global LV longitudinal strain** | 0.99 | <0.001 |
| **Global LV circumferential strain** | 0.96 | <0.001 |
| **LV strain rate** | 0.93 | <0.001 |
| **LV End diastolic pressure** | 0.90 | <0.001 |
| **Serum NT-proBNP** | 0.89 | <0.001 |
| **Global longitudinal strain of mid part** | 0.89 | <0.001 |
| **Global longitudinal strain of LV basal part** | 0.87 | <0.001 |
| **Global longitudinal strain of LV apical part** | 0.87 | <0.001 |
| **LV Wall thickness** | 0.85 | <0.001 |
| **LV End systolic volume indexed** | 0.80 | <0.001 |
| **LV ejection fraction** | 0.79 | <0.001 |

Three cut-off values for each test are presented in table 4 with their respective sensitivity, specificity, accuracy, and positive and negative predictive value, it showed that the best sensitivity presented in Global LV longitudinal strain, and best specificity presented in Global LV circumferential strain and Global LV longitudinal strain, the best accuracy presented in Global LV longitudinal strain and Global LV circumferential strain, (as illustrate in table 4).

**Table 4** Validity parameters for selected measurements prior to surgery when used as tests to predict an adverse outcome of surgery (Death or Dysfunctional heart)

| Predictors | Cut off value | SN | SP | AC | PPV* | NPV* |
|---|---|---|---|---|---|---|
| **LV End systolic volume indexed** | ≥49.5 | 70.3 | 82.1 | 77.9 | 79.7 | 96.1 |
| **LV End diastolic pressure** | ≥22.5 | 86.5 | 83.6 | 84.6 | 84.0 | 98.2 |
| **Serum NT-proBNP** | ≥1040.0 | 86.5 | 86.6 | 86.5 | 86.6 | 98.3 |
| **LV Wall thickness** | <12.5 | 86.5 | 74.6 | 78.8 | 77.3 | 98.0 |
| **LV ejection fraction** | <59.5 | 75.7 | 64.2 | 68.3 | 67.9 | 96.0 |
| **Global LV longitudinal strain** | <-16.2 | 97.3 | 92.5 | 94.2 | 92.9 | 99.7 |
| **Global longitudinal strain of LV basal part** | <-17.5 | 91.9 | 77.6 | 82.7 | 80.4 | 98.9 |
| **Global longitudinal strain of LV mid part** | <-15.5 | 81.1 | 82.1 | 81.7 | 81.9 | 97.5 |
| **Global longitudinal strain of LV apical part** | <-15.5 | 78.4 | 80.6 | 79.8 | 80.2 | 97.1 |
| **LV strain rate** | <1.6 | 89.2 | 85.1 | 86.5 | 85.7 | 98.6 |
| **Global LV circumferential strain** | <27.5 | 89.2 | 94.0 | 92.3 | 93.7 | 98.7 |
| **SN: Sensitivity, SP: Specificity, AC: Accuracy, PPV: positive predictive value, NPV: negative predictive value** | | | | | | |
| *** at equal odds pre-test probability of 50%** | | | | | | |

## 4. DISCUSSION

The behavior of left ventricular is crucial for the outcome of patient with CAD referred for CABG, it play important role for selection a candidate for the procedure, and predicting adverse outcome post-surgery. Many echo parameters can be easily obtained preoperatively that have strong predictive value not only for the immediate but also for mid, and late outcomes post CABG (Zdravkovic *et al.*, 2009).

The LV myocardial function was evaluated in the present study within a maximum of oneweek prior to surgery and within 8 to 24 weeks after CABG. In this way the temporary transient LV systolic dysfunction, which frequently occur several hours following cardiopulmonary bypass (CPB) will not affect the adverse outcomes of interest for the current work. Possible causes for this transient LV dysfunction includes: the effect of cardioplegia, myocardial ischemia, hypothermia induced vasoconstriction and reperfusion injury, all having potential impact on morbidity and mortality (Wallace *et al.*, 1994).

The main result of this study is that LV longitudinal & circumferential strain can predict the early adverse outcomes after surgery whether the LVEF was normal or low and whether serum NT-proBNP was normal or high. This indicate that both are helpful in discovering subtle LV systolic dysfunction which is determinant of post-operative adverse outcomes.

Since more than 50% of the patients included in the study are hypertensive so there will be increase in circumferential strain (which may be compensatory for decrease in longitudinal myocardial systolic strain) which is related to the elevation of LV mass (Przewlocka-Kosmala *et al.*, 2006). As consequence there will be false augmentation of LVEF missing with subtle LV systolic dysfunction in spite of preserved LVEF (heart failure with preserved LVEF), also 24% of the patients had reduced LV longitudinal and/or LV circumferential strain in spite of normal LVEF (HFPEF), 80% of those had early adverse outcomes. Many researchers like juelian *et al* confirm the above observation and proved the incremental value of LV longitudinal strain over LVEF for post-operative risk stratification of patients with CAD referred for CBAG (de Simone *et al.*, 1997). Yin et al concluded that speckle derived LV longitudinal & circumferential strain are more effective than LVEF, LVEDD and SV for monitoring improvement & outcomes in myocardial function post-CBAG (Yin *et al.*, 2013). Macron et al suggest that speckle derived LV global longitudinal strain & strain rate are correlated with LVEF assessed by cardiac MRI & not LVEF derived by echocardiography (Macron *et al.*, 2011).

This study showed that a value of LV longitudinal & circumferential strain (-17%), (-25%) are most accurate criteria for predicting adverse outcome with an accuracy of 92.3%, 89.4%.

Three parameters are associated with excellent (ROC area >0.9) namely LV global longitudinal strain, Strain rate, and circumferential strain. Their negative cut off value was for GLS≥(-16.5%), Circumferential strain ≥ (-36.5%), and for Global longitudinal strain rate ≥ $2.3s^{-1}$.

An EDWT <0.6 cm is highly associated with irreversible injury (negative predictive value 93%) and virtually excludes myocardium with potential for functional recovery. The positive predictive value of EDWT could be increased with the addition of biphasic response during dobutamine stress test (DSE), which implies limited coronary flow reserve. EDWT of <0.6cm in baseline echo can exclude the presence of significant viability with negative predictive accuracy similar to DSE. Rungroj et al compare the value of late gadolinium enhancement (LGE) and EDWT assessed by cardiovascular magnetic resonance (CMR) in predicting recovery of left ventricular function after CABG. The study demonstrated that with the cut-off of ≤ 5.5 mm, EDWT had a sensitivity and specificity of 70.1% and 81.5% in the prediction of functional recovery. Functional recovery was demonstrated in 26% of segments with EDWT ≤ 5.5 mm and 49.9% of segments with EDWT ≥ 5.5 mm. LGE area is a better predictor for functional recovery than EDWT and has a good predictive power even in patients with an EDWT ≤ 5.5 mm (Krittayaphong *et al.*, 2008). In this study, LV EDWT cut off value of ≥ 12 mm have 85.5% sensitivity, 76.6% specificity, 78.8% accuracy, negative predictive value of 100% in predicting adverse outcome post CABG.

Elevated LVEDP could predispose to mortality after cardiac surgery for several reasons. First, it is commonly associated with reduced left ventricular function. Second, one frequent cause of elevated LVEDP is left ventricular hypertrophy, a risk factor for diastolic dysfunction and a known surgical risk factor due to inadequate myocardial protection. Third, it is possible that patients with normal LVEF (systolic function) and elevated LVEDP which may deteriorate with abnormal loading conditions may render the patient very sensitive to peri-operative, hypovolemia on one hand and volume overload on the other. Finally, patients with elevated LVEDP could have associated secondary pulmonary hypertension, all are variable linked with increased morbidity and mortality in cardiac (Salem *et al.*, 2006).

Preoperative NT-ProBNP is a valuable marker in predicting postoperative mortality and bad outcome in patients undergoing heart surgery (de Simone *et al.*, 1997). Hutfless et al. considered complications and one-year mortality after heart surgery. A cut-off value above 2773.5 pg/ml was the best cut-off (sensitivity of 63.6% and specificity of 80.8%) to predict the mortality within 30 days of surgery (Hutfless *et al.*, 2004). Sodeck's research showed that an increased level of serum NT-pro BNP >647 pg/ml is associated with unfavorable outcome (Sodeck *et al.*, 2008). Schachner et al, conclude that elevated preoperative serum NT-proBNP levels are associated with a higher postoperative early and mid-term mortality, as well as morbidity, in patients undergoing isolated CABG. ROC curve analysis revealed an NT-pro BNP cut-off level of 430 ng/L is best predict for hospital mortality and a cut-off level of 502 ng/L best for prediction of overall mortality (Schachner *et al.*, 2010). Grescenzi et al. showed that postoperative NT-pro BNP levels are associated with in-hospital mortality and prolonged ICU stay after CABG surgery. Hua Liu et al demonstrated that a serum NT-proBNP of > 2773.5 pg/ml was the best cut-off (sensitivity of 63.6% and specificity of 80.8%) to predict the mortality within 30 days of surgery (Crescenzi *et al.*, 2009). In the current study cut off value which predict adverse effect is different, serum NT-proBNP value ≥1040 pg/ml was the optimum cut-off value (sensitivity of 86.5% and specificity of 86.6%) to predict adverse outcome after surgery. In addition a high serum NT-proBNP ≥ 500 pg/ml increase the prediction of adverse outcome in subjects with abnormally low LV strain values (circumferential and/or longitudinal) to 83.7% compared to only 25% for those with normal NT- proBNP and low LV

strain values. So the cut-off value of NT-proBNP in this study range between Sodeck's & Grescenzi. Based on the above argument the use of serum NT-proBNP is recommended as a routine preoperative assessment for predicting patients with postoperative risk because of it is convenient, quick and not expensive.

## 5. CONCLUSION

The mean LV longitudinal, circumferential strain & strain rate provides a valuable tool for selecting candidates for CABG±MVR assuring a plausible outcome after surgery.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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