Title: Evaluation of Myocardial Tissue Doppler Echocardiography as a Predictor for Recovery of Left Ventricular Function after Percutaneous Coronary revascularization for Patients with Coronary Artery Disease.

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Abstract:

<u>Background:</u> Trials postulate that analysis of pre-ejection velocities is closely sensitive to blood supply. Tissue velocities declines with reduced regional perfusion and recover on reperfusion. Accordingly, tissue doppler imaging (TDI) can predict myocardial function recovery after revascularization.

Purpose: To assess the value of Tissue Doppler Imaging echocardiography in predicting recovery of myocardial function after percutaneous coronary revascularization in patients with coronary artery disease (CAD.(

<u>Methods:</u> 27 patients with CAD based on coronary angiography were prospectively studied. Echocardiography with 2D measurements, global systolic function and longitudinal myocardial velocities; (IVCPv, S wave, AT, IVCT, CT and IVRT) of the affected segments were recorded 24 hours before revascularization and 6 months after revascularization. Functional recovery was defined as increase in LVEF by ≥ 5%.

<u>Results:</u> All patients underwent PCI. Most of TDI parameters changed significantly with revascularization, however only mean IVCPv and S wave of dysfunctional segments at rest correlated significantly with recovery of global systolic function. Mean IVCPv> 2.8 cm/sec and mean S wave > 4.6 cm/sec at baseline are an objective indicator of global systolic function recovery with sensitivity, specificity and accuracy for IVCPv (85%, 70%, 79% respectively) and PPV was estimated to be 80% (AUC=0.789, CI=0.603 -0.975, P value=0.02), while for S wave (87%, 77%, 83% respectively) and PPV was 87% (AUC=0.833, CI=0.664 -1.000, P value=0.007).

<u>Conclusions:</u> The resting pattern of IVCPv & S wave by TDI accurately predicts the recovery of global systolic function with high PPV but not the regional function after revascularization in patients with CAD.

Manuscript

INTRODUCTION

Coronary artery disease (CAD) is nowadays the leading cause of death in the world (45% of all Cardiovascular deaths) accounting for 12% of all deaths globally [(1)].

Despite the recent debate aroused by ISCHEMIA trial regarding revascularization of patients with stable ischemic heart disease[(2)] , There is upward interest in percutaneous treatment of patients with recent or recurrent acute coronary syndromes (ACS) due to enhancements in observational evidence that effective treatment of CAD is associated with significant revolutions in cardiac function and outcome[(3)]. The rationale for the recanalization is the expected increase of left ventricular (LV) function via the recovery of hibernating myocardium[(4)].

The concept of hibernating myocardium defined as ischemic myocardium supplied by a narrowed coronary artery in which ischemic cells remain viable but contraction is chronically weakened[(5)] has resulted in a significant contribution to clinical cardiology because it pointed out that chronic left ventricular dysfunction can be revocable. Indeed, the amount of dysfunctional, but viable myocardium is a key prognostic factor in patients with CAD and left ventricular dysfunction[(7)].

Various techniques are used to evaluate myocardial viability in patients with CAD. Cardiac magnetic resonance imaging or Nuclear imaging is highpriced, and frequently inaccessible for clinical decision-making. Furthermore, low-dose dobutamine echocardiography is highly operator dependent. In addition, 2-D echocardiography has been labelled as the supreme imaging modality for the evaluation of global and segmental ventricular function. However, conventional evaluation of wall motion by visual examination of endocardial excursion and myocardial thickening has the restraints of being subjective, qualitative method, and is operator dependent[9]. Therefore, the current methods for assessment of viability are time consuming, expensive or operator-dependent[8].

Tissue Doppler imaging (TDI) is an addition of conventional Doppler echocardiography; a change in the image attainment process enables straight measurements of myocardial tissue velocities. The initial application of TDI in quantifying myocardial mechanical motion was to measure the peak systolic and diastolic tissue velocities of the given segment with an excellent temporal resolution and the results have been encouraging so far[11].

Typical myocardial velocity display during the pre-ejection period consists of a positive wave often followed by a small negative wave reflecting the short inward and outward wall movement during this phase. Experiments suggest that analysis of pre-ejection velocities is highly sensitive to blood supply[12]. In addition, in an animal model of acute myocardial infarction (MI), perseverance of a positive velocity in reperfused dysfunctional segments denoted nontransmural necrosis[13].

Accordingly, wall motion can be quantified by TDI. Low systolic tissue velocities correlate with angiographic or echocardiographic wall motion abnormality[14]. Tissue velocities decrease with reduced regional perfusion, recover on reperfusion, and differentiate between transmural and nontransmural infarction[15–17].

METHODS

Our study prospectively enrolled 27 patients. Only 24 patients completed the study protocol while, unfortunately, three died during follow up.

Inclusion criteria

Patients enrolled are diagnosed with CAD based on previous diagnostic coronary angiography (CA) done before. They have impaired systolic function and regional wall motion abnormality (RWMA) on transthoracic echocardiography (TTE) and were eligible for percutaneous coronary intervention (PCI).

Exclusion criteria

Patient were excluded if they have poor echogenic window, proved non-viability by any image modality, significant valvular heart disease or preserved systolic function at baseline.

After obtaining approval by the Research Ethics Committee and written informed patient consent with an explanation regarding the purpose, methods, effects, and complications, the study was conducted in Suez Canal Univeristy Hospital, cardiology department.

A structured interview was used to collect the basic clinical data of the patient, and examination was done to all patients enrolled in the study including general and local cardiac examination with resting 12 lead ECG. Transthoracic echocardiography (TTE) was performed at baseline using General Electric Vivid 7 (GE Ultrasound, Horten, Norway) machine & Philips ie equipped with the TDI mode with 2–2.5 MHz transthoracic transducers were used. The American Society of Echocardiography (ASE) recommendations were followed regarding measurements of dimensions and global systolic function.

The conventional 2-D measurements including Left ventricular end systolic dimension (LVESD), Left ventricular end diastolic dimension (LVEDD), and global systolic function were measured. Tissue Doppler Imaging Pulsed Wave derived parameters (TDI-PW) of dysfunctional segments; namely Isovolumic contraction peak velocity (IVCPv), Systolic wave (S wave), Acceleration time (AT), Isovolumic contraction time (IVCT), Contraction time (CT), and Isovolumic relaxation time (IVRT) were identified and recorded on DVDs for offline analysis.

The 16-segment model was used with exclusion of apical segments (due to poor TDI image quality) and scoring system was followed on grading segments' dysfunction and wall motion scoring index (WMSI) was calculated for each patient. All the patients had undergone revascularization by PCI with a drug-eluting stents.

After 6 moths, another follow-up echocardiography was done with all same baseline measurements were recorded again and were compared with baseline data.

RESULTS

Patients characteristics

The present study investigated whether TDI-derived myocardial Preejection velocities can predict recovery of contractile function after revascularization of a dysfunctional territory. **Table 1** summarizes the patient's main characteristics at baseline.

Table 1. Baseline main characteristics:

parameters	**Baseline characteristics**
Age (years) (mean ±SD)	57.1 (±9.1)
Gender	
• Males (%)	13 (54.2)
• Females (%)	11 (45.8)
BMI (Kg/m2)	27.1 (±3.5)
Smoking (%)	13 (54.2)
Hypertension (%)	16 (66.7)
Diabetes Mellitus (%)	10 (41.7)
Dyslipidemia (%)	18 (75)
Family History (%)	1 (4.2)
Single Vessel-CAD (%)	7 (29.2)
Two Vessel-CAD (%)	6 (25)
Three vessel-CAD (%)	11 (45.8)
Heart rate (bpm) at baseline (mean ±SD)	77 (±10)
LVEF % (mean ±SD)	48.5 ±5 (range, 35 to 52)
Wall motion score index	1.59 (±0.3)

BMI; Body mass index, bpm; beat per minute, CABG; coronary artery bypass graft, CAD; Coronary artery disease, PCI; percutaneous coronary intervention, LVEF; Left ventricular ejection fraction.

Twenty-seven patients (11 females, 13 males, and 3 died during follow up). The mean age was 57 years. The left ventricular ejection fraction (LVEF) at baseline ranged from 35% to 52% (mean was 48.5%) which dramatically improved with revascularization to a mean of 54.8% (P value<0.001). Dyslipidemia, hypertension, smoking and diabetes were prevalent risk factors among patients representing (75%, 66%, 54% and 42% respectively). About half of patients (45.8%) have three vessel disease while seven patients have single vessel disease and six patients have two vessel disease. Wall motion score index was calculated as the sum of score of each segment [normal (1), hypokinetic (2), Akinetic (3), Dyskinetic (4)]/ total number of visualized segments (12 segment). It improved significantly 6 months post revascularization from 1.59 to 1.12 (P value< 0.001).

From all TDI-PW derived parameters, only mean IVCPv and mean S wave velocity of dysfunctional segments at baseline correlate significantly with changes in LVEF (global functional recovery) with revascularization as shown in **Table 2**.

Table 2. changes in conventional echocardiography parameters at baseline and at 6 months post revascularization among patients:

Parameters	Baseline (mean ±SD)	At 6 months (mean ±SD)	P- Value*
LAD (mm)	39.75 (±2.5)	43.13 (±3.9)	0.0001
LVEDD (mm)	50.04 (±7.5)	56.46 (±4.5)	0.0001
LVESD (mm)	43.75 (±8.9)	40.75 (±4.9)	0.071
EF%	48.58 (±4.8)	54.75 (±4.9)	0.0001
FS%	26.53 (±3)	29.26 (±2.8)	0.0001
WMSI**	1.59 (±0.3)	1.12 (± 0.3)	0.0001

AOD, aortic root diameter; EF, ejection fraction; FS, fraction shorting; LA, left atrial diameter; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; WMSI, wall motion score index.
*Statistically significant difference (p-value < 0.05).
NS: No statistically significant difference (p-value > 0.05).

TDI-derived parameters and recovery of global function (LVEF):

There is a significant difference between mean of both IVCPv and S wave of dysfunctional segments at baseline among patients who showed significant improvement in LVEF 6 months after revascularization versus those patients who didn’t exhibit significant improvement (2.8±0.4 vs. 3.5±0.8 for IVCPv, and 4.5±0.9 vs 5.8±1.1 for S wave, p value <0.05 and <0.01 respectively) as shown in **Table 3**.

Table 3. Relationship between mean TDI parameters of dysfunctional segments for all patients at baseline versus recovery of global systolic function.

Parameter	Δ LVEF [%]*	Mean ±SD**	P value
IVCPv (cm/s)	No recovery Recovery	2.8 (±0.4) 3.5 (±0.8)	0.03
S wave(cm/s)	No recovery Recovery	4.5 (±0.9) 5.8 (±1.1)	0.005
IVCT (m/s)	No recovery Recovery	89.6 (±16) 103.75 (±25)	0.1
CT (m/s)	No recovery Recovery	266.9 (±22) 278.8 (±22)	0.2
AT (m/s)	No recovery Recovery	40.1 (±8.7) 43.8 (±8.5)	0.3
TP (m/s)	No recovery Recovery	121.6 (±20.9) 130.6 (±24.9)	0.3
IVRT (m/s)	No recovery Recovery	128.7 (±31.3) 125.9 (±28.4)	0.8

AT, acceleration time of isovolumic contraction; CT, contraction time; IVCPv, isovolumic contraction peak velocity; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; S wave, contraction wave velocity; TP, time to peak isovolumic contraction.

There is significant moderate positive correlation between mean IVCPv and mean S wave velocity at baseline and changes in LVEF (global functional recovery) with revascularization (p value<0.05 and <0.01 respectively).

The mean systolic (S) velocity showed a cutoff value of 4.6 cm/s (AUC=0.833, CI=0.664 -1.000, P value=0.007) or more for prediction of recovery of global systolic function with a sensitivity, specificity and accuracy of 87%, 77% and 83% respectively **(Table4)**.

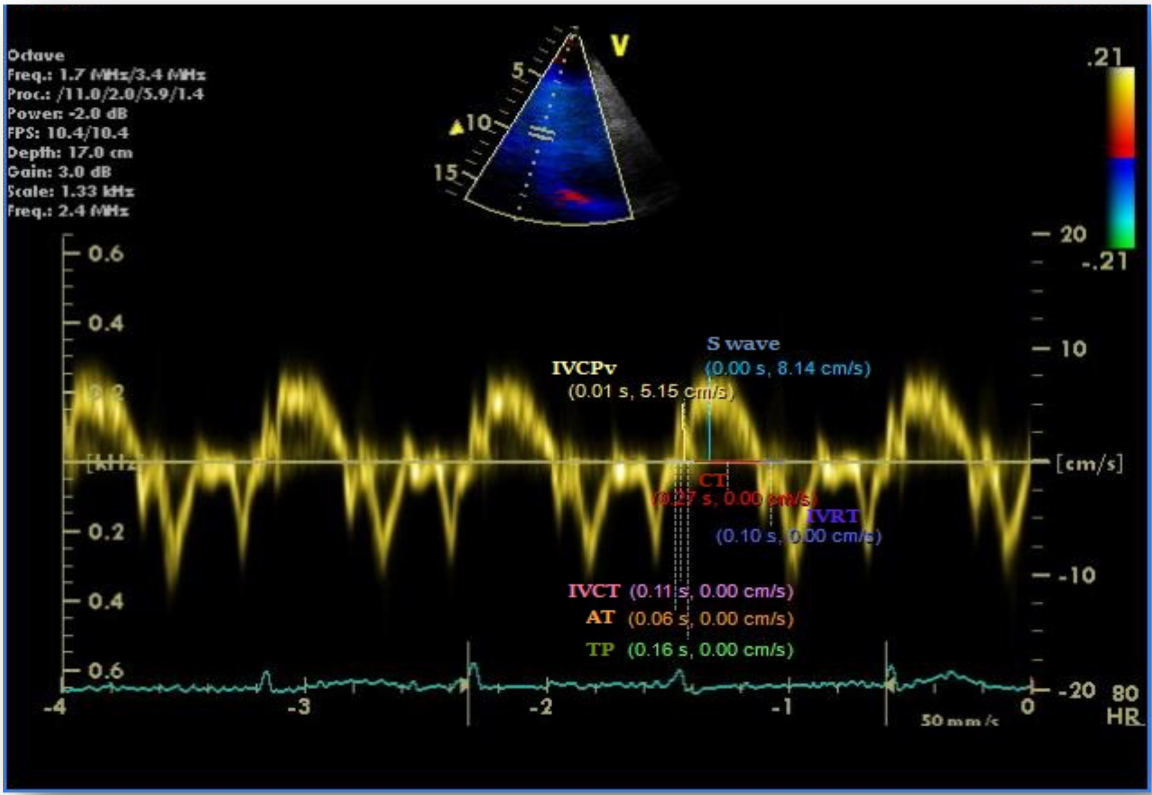
Table 4. Relationship between mean TDI parameters of dysfunctional segments for all patients at baseline versus recovery of global systolic function.

Parameter		Δ LVEF		
		Improved (≥5%)	Not improved (<5%)	Total
IVCPv (cm/s)	Positive (≥ 2.86)	12	3	15
	Negative (< 2.86)	2	7	9
	Total	14	10	24
S wave (cm/s)	Positive (≥ 4.6)	13	2	15
	Negative (< 4.6)	2	7	9
	Total	15	9	24

IVCPv, isovolumic contraction peak velocity; S wave, contraction wave velocity;

The mean IVCP velocity showed a cutoff value of 2.86 cm/s (AUC=0.789, CI=0.603 - 0.975, P value=0.02) or more for prediction of recovery of global systolic function with a sensitivity, specificity and accuracy of 85%, 70% and 79% respectively **(Table4)**.

Multivariable regression analysis showed that only IVCPv and mean S wave velocity of dysfunctional segments are independent predictors of global functional recovery (LVEF) with overall sensitivity, specificity and accuracy of mean IVCPv were 85%, 70% and 79% respectively. While that of S wave velocity were 87%, 77% and 83% respectively. The positive predictive value (PPV) and negative predictive value (NPV) for mean IVCPv were 80% and 77% for IVCPv versus 87% and 77% for S wave **(Figure 1A, 1B).**



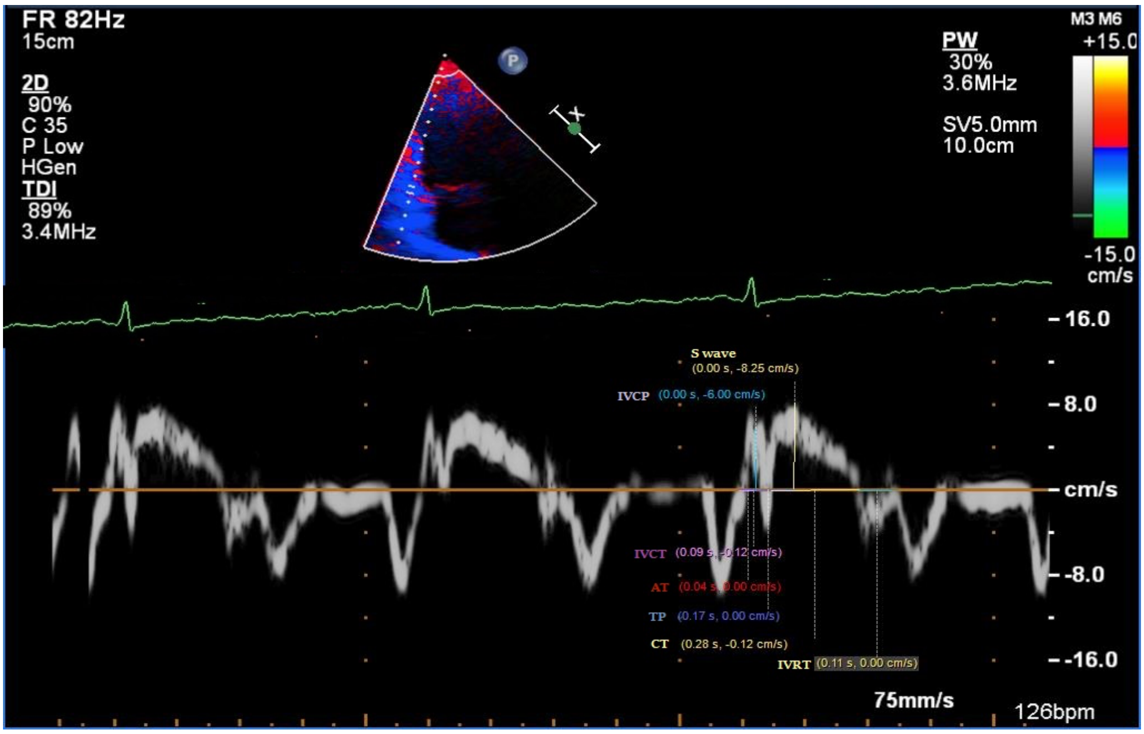


Figure 1A, 1B. A case of occlusion-RCA before (1A) and after Percutaneous coronary intervention (1B) tissue Doppler imaging (TDI): shows changes in TDI parameters values before and after PCI in basal inferior wall.

DISCUSSION

Coronary artery disease with consequent left ventricular (LV) dysfunction is one of the chief underlying causes of heart failure (HF) with significant morbidity and mortality. Therapeutic trials to improve the outcome of these patients witnessed a great evolve over the past decades and included a multidimensional approach aimed at relieving symptoms and improving ventricular function, together with reducing reinfarction and sudden Cardiac death, using multidrug therapy and revascularization procedures[19].

The motivation for the reopening of coronary occlusion is the possible increase in LV function through the recovery of hibernating myocardium[5].

Several echocardiography techniques are promising for assessment of myocardial viability, among those is tissue Doppler imaging, which can measure several different parameters of myocardial contraction, similarly has been shown to have promising accuracy for objective viability assessment[20].

The primary aim of this study was to assess the value of tissue Doppler imaging echocardiography derived pulsed wave parameters at rest to predict left ventricular contractile recovery in patients undergoing percutaneous coronary revascularization. The objectives of study were; (1) To address the correlation between parameters of TDI and improvement of both LV global and regional function after Percutaneous Coronary Revascularization, and (2) To determine sensitivity, specificity and accuracy of TDI in predicting myocardial recovery.

Conventional echocardiography and systolic function:

Global systolic recovery was defined as increase in LVEF by ≥ 5%. Recanalization of occluded vessel(s) was associated with significant improvement of LVEF ≥ 5% (recovery) from 48.6±4.8 at baseline to 54.7±4.9 six month after PCI (p <0.001), and this is reflected on significant improvement of resting wall motion score index from 1.59±0.3 at baseline to 1.12±0.3 after 6 months (p <0.001).

Cardona M. et al.[(21)] showed an increase in LVEF (31.3 ± 7.4 % vs. 37.7 ± 8 %; p < 0.001) 6 months after PCI. Also, the number of segments showing perfusion defects was significantly reduced (0.5 ± 1 vs. 0.2 ± 0.5; p = 0.043). This comes in agreement with another study Wessam H. El Shafeya, et al.[(5)] who used tissue doppler imaging to assess left ventricular function before and after PCI to Chronic total occlusion (CTO). A third study by Mobarock M., et al.[(22)] showed significant increase in LVEDD and LVESD with consequent improvement LVEF after intervention from (54.3±5.8) to (56.2±4.7), p value (<0.001).

To conclude, successful reopening of coronary occlusions is associated with a statistically significant increase in LV function. the mechanisms by which PCI of an occluded infarct related artery could recover LVEF include reduction in unfavorable LV remodeling with salvation of LV function, increased electrical stability, and provision of collateral vessels for protection against future events and recovery of hibernating myocardium[(207,208)].

Our results were corresponding to results reported by Rashid H. et al.[23] where mean systolic (S) velocity showed a cutoff value of 4.83cm/sec or more (compared to 4.6 or more in our study) for prediction of recovery of global systolic function with a sensitivity and specificity of 100% and 90% respectively while the positive predictive value, negative predictive value and accuracy were 97.5%, 100%and 0.986 respectively[23].

In a large study by Penicka M et al. (2007)[24] Patients were assigned to receive either optimum medical therapy or CABG surgery within 1 month of enrolment. They found that in medically treated patients, TDI-derived +Vic showed high sensitivity (91%) and specificity (85%) for the identification of viable myocardium compared with the three reference techniques. In patients who underwent CABG surgery, 66% of the 442 dysfunctional segments identified showed functional recovery at 6 months' follow-up, with high sensitivity (93%) and specificity (77%) of +Vic for the prediction of functional recovery. Multivariate analysis showed that the presence of +Vic was a significant and independent predictor of a moderate (≥5%) and distinct (≥10%) increase in LVEF (odds ratio [OR] 2.51, 95% CI 1.39–4.53; P = 0.001 and OR 2.12, 95% CI 1.32–3.42; P = 0.001, respectively).[24]

Summary and conclusion

First of all; significant improvement in global and regional LV function as measured by PW-TDI in patients with CAD after successful recanalization by PCI could occur. Second, most of Tissue Doppler imaging pulsed wave derived parameters (namely; Isovolumic contraction peak velocity and Systolic contraction wave peak velocity, isovolumic contraction time, and isovolumic relaxation time) change significantly with revascularization. Third, Only mean IVCPv and S wave of dysfunctional segments at rest correlate significantly with recovery of global systolic function.

Finally; Isovolumic contraction peak velocity (IVCPv) of dysfunctional segments measured at rest is an objective indicator of global systolic function recovery after PCI with acceptable sensitivity, specificity and accuracy (85%, 70%, 79% respectively). The PPV was estimated to be 80% indicating that most of patients meeting the criteria of mean IVCPv > 2.8 m/cm2 at baseline will truly show improvement of global systolic function, besides its NPV was estimated to be 77% indicating that any negative results may need further testing. On the other hand, it cannot predict contractile recovery of dysfunctional segments after PCI.

Systolic contraction wave velocity (S wave) an objective indicator of global systolic function recovery after PCI with better sensitivity, specificity and accuracy than IVCPv (87%, 77%, 83% respectively). The PPV was estimated to be 87% indicating that most of patients meeting the criteria of mean S wave > 4.6 m/cm2 at baseline will truly show improvement of global systolic function, besides its NPV was estimated to be 77% indicating that any negative results may need further testing. On the other hand, it cannot predict contractile recovery of dysfunctional segments after PCI. (regional contractile function).

To conclude, our study indicates that the resting pattern of myocardial IVCPv & S wave by TDI truthfully predicts the recovery of overall systolic function with high PPV but not the regional function after revascularization in patients with CAD. The detection of pre-ejection velocities by TDI is a practicable and acceptably reproducible technique that is freely available in our daily clinical practice.

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