Non-invasive imaging in detecting myocardial viability: Myocardial function versus perfusion

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A B S T R A C T

Coronary artery disease (CAD) is the most prevalent and single most common cause of morbidity and mortality [1] with the resulting left ventricular (LV) dysfunction an important complication. The distinction between viable and non-viable myocardium in patients with LV dysfunction is a clinically important issue among possible candidates for myocardial revascularization. Several available non-invasive techniques are used to detect and assess ischemia and myocardial viability. These techniques include echocardiography, radionuclide images, cardiac magnetic resonance imaging and recently myocardial computed tomography perfusion imaging. This review aims to distinguish between the available non-invasive imaging techniques in detecting signs of functional and perfusion viability and identify those which have the most clinical relevance in detecting myocardial viability in patients with CAD and chronic ischemic LV dysfunction. The most current available studies showed that both myocardial perfusion and function based on non-invasive imaging have high sensitivity with however wide range of specificity for detecting myocardial viability. Both perfusion and function imaging modalities provide complementary information about myocardial viability and no optimum single imaging technique exists that can provide very accurate diagnostic and prognostic viability assessment. The weight of the body of evidence suggested that non-invasive imaging can help in guiding therapeutic decision making in patients with LV dysfunction.

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1. Introduction

Because of high mortality rate and increasing prevalence of heart failure and the need to tailor therapy to the etiology and stage of the condition, testing of patients with heart failure will become increasingly common [2]. Non-invasive imaging can help identify viable segments of myocardium that have greater likelihood of improving functionally when an adequate blood supply is restored. Echocardiography, radionuclide images, cardiac magnetic resonance imaging and recently myocardial computerized tomography perfusion imaging are used to detect and assess ischemia and myocardial viability. These imaging modalities detect signs of myocardial viability through contractile reserve in response to low dose dobutamine, intact cell membrane or residual glucose utilization.

2. Definition and historical perspective of myocardial viability

Myocardial viability is the myocardium with a potentially reversible contractile dysfunction in patients with chronic CAD. Myocardial stunning is defined as a prolonged contractile myocardial dysfunction after a transient acute ischemia, whereas dysfunctional myocardium which improves after coronary revascularization is defined as myocardial hibernation [3,4]. Myocardial viability has been clinically recognized for more than 40 years ago. The term 'myocardial viability' adopted by clinicians relies on a clinical phenomenon that is potentially salvageable with treatment using revascularization, drugs or devices. The prognostic benefit is measured by patient's survival and symptomatic improvement or with cardiac function measurements.

For more than four decades, several observational trials have identified the reversible myocardial dysfunction post revascularization in patients with CAD and showed that ischemic LV dysfunction is not always irreversible. In 1973, Chatterjee et al. reported improved myocardial wall motion abnormalities following revascularization in the CAD patients in the absence of myocardial scar [5]. A year later, Horn et al. (1974) concluded that myocardial wall motion abnormalities improved by inotropic stimulation with epinephrine infusion in patients with CAD and LV asynergy [6]. Rahimtoola and Braunwald in the mid eighties used the term myocardial hibernation to describe a condition of abnormal resting ventricular function because of chronic hypoperfusion in CAD patients [3,4,7,8]. As a result of coronary blood flow reduction, acute and chronic adaptations of the myocardium prevent irreversible myocardial damage.

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3. Imaging techniques employed for viability assessment

Several non-invasive imaging modalities are used to assess myocardial viability and to identify markers of functional recovery. These imaging modalities have different diagnostic accuracy and limitations [9]. Assessment of systolic function and contractile reserve within areas of dysfunction are based on the imaging of dysfunctional myocardium using dobutamine stress echocardiography, Doppler tissue imaging and dobutamine stress cardiac magnetic resonance (CMR). Assessment of perfusion is based on the documentation of cell integrity using contrast echocardiography and nuclear techniques (SPECT and PET) by perfusion tracers or a combination of metabolic and perfusion tracers, respectively. Moreover, delayed enhancement CMR imaging and more recently multi slice computer tomography (MSCT) delayed enhancement imaging can define necrotic myocardium. For diagnostic and prognostic viability assessment, the relative merits of non-invasive myocardial function imaging as compared to myocardial perfusion imaging are discussed.

3.1. Non-invasive myocardial function imaging

3.1.1. Dobutamine stress echocardiography

Dobutamine stress echocardiography (DSE) is the most widely used modality and most extensively studied test for the assessment of myocardial viability. Contractile reserve is the most common criterion used to detect viable myocardium. Usually low dose Dobutamine is used by infusion of 5–10 mcg/kg/min Dobutamine which increases contractility in dysfunctional but viable myocardium while nonviable myocardium does not show this contractile reserve. In 1997 a meta-analysis by Bax et al. pooled 37 studies showed an overall sensitivity of 84% and specificity of 81% as compared with other imaging techniques, DSE has an overall similar sensitivity and the highest specificity [10]. In addition, pooled data by Bax et al. (2001) evaluated the detection of hibernating myocardium and utilized myocardial perfusion images and DSE [11]. However, most of these studies did not compare imaging techniques in the same patients [12]. FDG-PET, reinjection thallium SPECT, and DSE had the highest negative predictive values while rest–redistribution thallium SPECT and technetium sestamibi SPECT had lower values. The highest positive predictive value was seen with DSE with intermediate values for other forms of radionuclide myocardial perfusion imaging of 84% versus 75% except reinjection thallium SPECT which had the lowest value. However, DSE had the lowest negative predictive values in comparison with FDG-PET and reinjection thallium SPECT of 69% versus 80%. Furthermore, for the prediction of an improvement in LV ejection fraction (EF) after revascularization, DSE had the highest positive and negative predictive values compared with nuclear imaging (77% versus 70% and 85% versus 78%, respectively) [11]. Similar results have recently been confirmed by Schinkel et al. (2007) [13].

3.1.2. End diastolic wall thickness

End diastolic wall thickness (EDWT) may provide the simplest method to identify myocardial viability. This approach uses a cut-off value of ≥5.5–6 mm in most studies to determine whether a segment is viable [14]. Echocardiography and CMR can be used to measure the EDWT with the advantage of CMR that provides accurate measurements of the entire LV wall. In a meta-analysis study that used echocardiography and nuclear imaging [15], EDWT predicted functional recovery with a sensitivity of 94% but low specificity of 48% which were comparable to CMR-based wall thickness measurements results reported in a recent meta-analysis [16].

3.1.3. Myocardial strain imaging

More information on myocardial viability can be obtained by strain and strain rate. Strain is the deformation of an object relative to its original length and strain rate is the gradient of velocities between two points in space. Strain and strain rate imaging can be obtained either from color tissue Doppler imaging or 2D speckle tracking [17]. Echocardiography and CMR can be used to quantify myocardial strain and strain rate. Strain rate imaging, 2D speckle tracking and myocardial tagging may improve accuracy in detecting myocardial viability. In a study by Hoffmann R et al. (2002), strain rate imaging in combination with low dose dobutamine was used to improve assessment of viable myocardium in 37 patients with ischemic cardiomyopathy. An increase of peak systolic strain rate of ≥0.23/s had a sensitivity of 83% and specificity of 84% [18]. In addition, adenosine speckle tracking could be used to discriminate viable from non-viable myocardium with stress. In a recent small trial by Ran et al. (2012), 36 patients who had sustained previous MI and EF of 40% (±6%) were assessed and showed that using adenosine stress, radial myocardial strain more than 9.5% had a sensitivity of 83.9% and a specificity of 81.4% for detecting viable myocardium, whereas a change of longitudinal strain more than 14.6% displayed a sensitivity of 86.7% and a specificity of 90.2%. Peak-systolic circumferential strain however, had little effect on viability assessment. The study concluded that 2D speckle tracking imaging combined with adenosine stress echocardiography could be reliable method to detect viable myocardium [19].

3.1.4. Dobutamine stress CMR

Dobutamine stress CMR is based on the same principle as in the DSE that determines the contractile reserve of dysfunctional myocardium by administrating low dose dobutamine of 5–10 mcg/kg/min, viable myocardium will show an increased contractile function and non-viable myocardium will remain unchanged [20]. A recent meta-analysis by Romero et al. (2012) pooled nine studies assessing low dose dobutamine stress CMR showed that mean weighted sensitivity and specificity for low dose dobutamine stress CMR were 81% and 91%, whereas the PPV and NPV were 93% and 75%, respectively. Low dose dobutamine stress CMR showed the highest specificity in comparison with LGE and end-diastolic wall thickness [16].

Low dose dobutamine stress CMR and DSE are comparable as shown by Baer et al. (2000) in head to head study comparing dobutamine stress CMR and dobutamine stress transoesophageal echocardiography for predicting recovery of ventricular function post revascularization in patients with chronic CAD [21]. Both tests were highly accurate where the respective values of sensitivity and specificity for echocardiography were 82% and 83%, whereas for the CMR were 86% and 92%, respectively. A small study by Wellnhoffer et al. enrolled 29 patients suggested that low dose dobutamine stress CMR was superior to LGE in predicting improvement in wall motion of dysfunctional segments with 1–74% transmural extent of myocardial infarction after revascularization [22]. In addition, a study by Bove et al. demonstrated a similar improvement in percentage of wall thickness and LV function with low dose dobutamine in segments with 1–50% transmural infarction after revascularization [23]. Other studies suggested that the combination of LGE and low dose dobutamine stress CMR may offer a more reliable method of assessing myocardial viability [24,25]. A recent study demonstrated that combination of CMR viability parameters, contractile reserve by low dose dobutamine, EDWT and scar quantification improved the prediction of function recovery [26].

3.2. Non-invasive myocardial perfusion imaging

3.2.1. Myocardial contrast echocardiography

Myocardial contrast echocardiography (MCE) uses intravenous contrast agents composed of high molecular weight inert gases which produce microbubbles which behave like red blood cells and stay in the vascular space thus allow direct visualization of myocardial perfusion. The intensity of myocardial contrast reflects the myocardial blood flow. Therefore, dysfunctional segments are classified as viable when segments have normal or patchy perfusion and nonviable when segments have no perfusion [15].

MCE is used to assess myocardial viability and can distinguish stunning from necrotic tissues [27]. Microvascular integrity is a prerequisite of the technique to detect myocardial viability in dysfunctional segments. It has been shown that after acute myocardial infarction (MI), MCE has a high sensitivity and NPV of >90% in predicting functional recovery with low specificity (65%) but better than with SPECT imaging [28]. Recently, a review by Hayat et al. (2008) in the setting of ST-elevation MI showed that MCE had a high sensitivity of 82% for predicting functional recovery after revascularization but equivalent specificity compared with DSE. MCE and cardiac MRI were comparable in predicting functional recovery [29].

MCE has also been used to assess myocardial viability in patients with chronic LV dysfunction. MCE using direct intra-coronary injections of microbubbles has been compared with DSE and thallium-201 rest redistribution SPECT in 18 patients undergoing revascularization. MCE and rest SPECT had high sensitivity for detecting a hibernating myocardium ranging from 62% to 92% and a low specificity from 67% to 87% for predicting regional functional recovery compared with DSE [30]. A study by Shimoni et al. using quantitative intravenous MCE showed that MCE has a high sensitivity of 90% which was similar to Tl-201 SPECT (92%) and superior to DSE (80%); the specificity was higher for MCE (63%) than for Tl-201 SPECT and DSE (45% and 54%, respectively) [31]. Therefore, generally MCE is sensitive but not specific for the prediction of functional recovery. However, the specificity can be improved by integrating MCE and DSE to allow more information on perfusion and contractile reserve thus high likelihood to improve in function after revascularization [32,33].

3.2.2. Single-photon emission computed tomography (SPECT)

SPECT is one of the non-invasive nuclear imaging techniques most frequently performed to detect myocardial viability. Viable myocardium is identified by demonstrating the myocyte membrane integrity through the extent of myocardial uptake of the radioactive tracers. The radioactive tracers used in clinical practice include Thallium-201 or Technetium (Tc)-99 m or Tc-99 m tetrofosmin, with Tc-99 m sestamibi being the most widely used tracer in clinical practice.

Several comparative studies with thallium reinjection and PET imaging with FDG demonstrated a correlation between viable segments defined by thallium reinjection and the metabolic evidence of viable myocardium defined by PET [34]. It has been shown that Technetium-99 m sestamibi has lower predictive values compared with thallium-201 [35] but in other studies Technetium-99 m sestamibi and thallium-201 were comparable in predicting functional recovery [36]. Recently, Schinkel AF et al. (2007) analysis of 24 studies using thallium-201 SPECT and technetium-99 m sestamibi SPECT in predicting segmental functional recovery after revascularization showed a similar high sensitivity of 87% (range 76%–96%) versus 83% (range 72%–96%), respectively whereas technetium-99 m sestamibi SPECT had a better specificity than thallium-201 SPECT of 65% (range 53%–88%) versus 54% (range 25%–65%) [13].

3.2.3. Positron Emission Tomography (PET)

Cardiac PET detects myocardial viability by using a combined perfusion assessment with Nitrogen-13 labeled ammonia ($^{13}NH_3$) or Rubidium-82 or Oxygen-15 water that quantify myocardial blood flow and metabolic assessment with Fluorine-18-deoxyglucose (FDG-18). The most commonly used technique is by combined perfusion ($^{13}NH_3$) and metabolic FDG-18 PET "tracer combination technique". PET is considered highly accurate in diagnosing myocardial perfusion abnormalities [15].

Over the years, many studies employed nuclear imaging comparing the perfusion SPECT technique with metabolic PET technique; most of these studies concluded equivalent results. Bonow et al. (1991) reported an 88% concordance between stress, delayed, and reinjection Tl-201 and 18F-FDG-PET imaging. Regions with mild to moderate Tl-201 defects were viable and also had metabolically viable myocardium

with FDG-18 PET [34]. Siebelink et al. (2001) found no difference in patient management or cardiac event-free survival when compared (^{13}N)-ammonia or 18F-FDG PET guided management with stress or rest Tc-99 m sestamibi SPECT guided management. They suggested that in management decision both imaging techniques were comparable and may be used for viability detection [37].

In a pooled 19 studies based on six PET and 13 SPECT, thallium SPECT compared to PET showed higher sensitivity with high NPV of 90% versus 83% and lower specificity with low PPV of 69% versus 82%, respectively in predicting recovery of ventricular function [38]. A meta-analysis by Allman et al. (2002) of 24 observational studies involving 3088 patients showed that both nuclear imaging had a similar ability to predict a survival benefit after revascularization [39]. However, there were studies showing that the detection of viability by metabolic PET had higher sensitivity and specificity than perfusion SPECT. Rohatgi et al. reported that PET detect a significant amount of viable myocardium in almost 60% of ischemic cardiomyopathy patients which indicated by thallium SPECT as a scar, in addition to a significant improvement in survival after revascularization in compared to medical treatment alone [40].

In 2004, a meta-analysis by Underwood SR et al. found that both SPECT and PET demonstrated high sensitivity [12]. The recent analysis by Schinkel AF et al. (2007) pooled 24 studies (756 patients) noted that PET had highest sensitivity compared with SPECT with weighted mean sensitivities and specificities of 92% and 63%, respectively, and higher positive and negative predictive values of 74% and 87% respectively for the prediction of regional ventricular function post revascularization [13].

3.2.4. Late-gadolinium enhancement CMR (LGE-CMR)

Contrast enhanced CMR with gadolinium was first described in 1984 and has proved useful in detecting infarcted tissue, which appear hyper enhanced. Kim et al. first demonstrated the potential of LGE-CMR in the assessment of myocardial viability over a decade ago. They demonstrated hyper enhancement in acute and chronic myocardial infarcted areas while no hyper enhancement in the reversible damaged myocardial areas was seen [41]. In 2000, they found that the likelihood of functional recovery of the myocardium after revascularization decreased progressively as the transmural extent of LGE before revascularization increased [42]. In a meta-analysis by Romero et al. (2012), LGE CMR demonstrated the highest sensitivity of 95% with specificity of 51%, PPV of 69% and NPP of 90% for predicting regional wall motion improvement after revascularization [16]. In 2007 a prospective cohort trial (29 patients) demonstrated that LGE-CMR and PET/SPECT were equally effective in determining myocardial viability [43]. Furthermore, several studies have supported the latter finding and have additionally demonstrated that LGE-CMR is superior to DSE in certain patients, including those with poor images or arrhythmias for the detection of viability [25,44].

3.2.5. Multi slice computerized tomography

Multi slice CT (MSCT) technology has been introduced to assess myocardial viability due to recent advances in its temporal and spatial resolutions. Several studies in patients with MI compared the accuracy of the late contrast enhanced CT with LGE CMR demonstrated a similar accuracy in the detection of myocardial viability [45,46], although, a systematic underestimation of infarct size by MSCT have reported [47]. In addition, delayed enhancement and early perfusion defects on MSCT can predict myocardial function recovery three months after acute MI. Delayed enhancement MSCT had a respective sensitivity and specificity of 73% and 85% whereas early perfusion defects had a sensitivity and specificity of 57% and 90%, respectively [48]. Compared with SPECT, MSCT has also been shown to accurately detect healed MI [49]. Moreover, when compared with DSE and SPECT, LV with >75% segmental extent of infarcted myocardium by MSCT were correlated to the decreased uptake by SPECT and contractile reserve by DSE [50].

4. Applicability of viability data in predicting functional outcome

Observational studies employing non-invasive imaging in patients with ischemic LV dysfunction have pointed out toward detection of myocardial viability as a target for prognostic revascularization and other therapies. Despite that many of these studies were small, from a single center, predated the advent of current medical and device therapies for heart failure and predated the new modalities such as PET and CMR but these studies emerge data regarding improvements after revascularization. Several clinical endpoints tested by non-invasive imaging modalities improved after revascularization including regional LV improvement, global LV improvement in the form of LV EF, heart failure symptoms (NYHA class) and exercise capacity in addition to reverse LV remodeling as well as survival benefit.

Predicting improvement in LV function was evaluated in a meta-analysis by Schinkel AF et al. (2007) that analyzed the prediction of improvement of regional contractile function after revascularization [13]. Individual technique mean sensitivity and specificity was: DSE, 74% and 82%; SPECT, 83%–87% and 54%–68%; PET, 92% and 63%; LGE-CMR, 84% and 63% and dobutamine stress CMR, 88% and 87%. Nuclear techniques tended to have higher sensitivity and low specificity as compared to DSE. However, many studies evaluated regional LV improvement after revascularization rather than global (LV ejection fraction) improvement [13]. From a clinical perspective, global LV improvement and eventually survival improvement are more important than regional LV recovery [15]. The meta-analysis published by Underwood et al. demonstrated an improvement in LV ejection fraction in patients with viable myocardium whereas no change in those without hibernation [12].

In addition, improvement of symptoms and exercise capacity correlated with the extent of viable myocardium after revascularization [13]. However, Marwick and colleagues (1999) failed to demonstrate a relation between PET assessed viability and improvement of exercise capacity after revascularization [51]. Furthermore, improvement of LV geometry of viable myocardium after revascularization contributes to better LV systolic function, which subsequently improves patient's prognosis [52]. Indeed, patients with evidence for viable myocardium and large LV size demonstrated a high event rate (67%) as compared to those with viable myocardium and small LV size (5%) [53].

Survival benefit after revascularization in patients with defined viability by any imaging modalities was observed in several pooled analyses [37,54]. A recent meta-analysis pooled 9 studies using PET showed the highest mortality rate in patients with viable myocardium who were treated medically compared to those who were revascularized [55]. Similar survival benefit was noted in another review by Underwood SR et al. (2004) in patients with viable myocardium after revascularization in which annual mortality rate was reduced by 7% versus 20% in medically treated patients [12].

The large body of data comes from a meta-analysis by Allman et al. (2002) of 24 observational studies involving 3088 patients demonstrated that medically treated patients with defined viability by echocardiography, SPECT and PET compared to non-viable group had an annual death of 16% versus 6.2%, respectively. Patients with evidence for viable myocardium on all imaging techniques had a reduced rate of death by 79.6% compared to those without evidence of viable myocardium after revascularization, with an annual death of only 3.2% in the former compared with 7.7% in the latter [39]. Similarly, the most recent retrospective study using PET imaging demonstrated that a survival benefit was better with revascularization than with medical therapy in patients with >10% hibernating myocardium [56].

The viability imaging findings from previous observational and retrospective studies have been recently challenged by surprising contradictory findings from prospective, randomized trials of a sub-study of the prospective Surgical Treatment of Ischemic Heart Failure (STICH) trial and the Canadian PPAR study [57,58]. Both studies

reported a lack of this association between the presence or absence of residual myocardial viability and patient's mortality outcome when treatment was allocated to revascularization or medical therapy. However, several study limitations with potentially confounding effects may explain the seemingly contrary results, and further trials are needed to explore this outcome.

5. Clinical implications

It has been shown that patients with chronic ventricular dysfunction and CAD have poor long term survival. Identification of such patients who may benefit from revascularization procedures is the major goal to improve outcomes. Several viability studies have estimated the long term prognosis as a final endpoint and concluded that viable myocardium was related to the improvement in myocardium function.

In addition, selection of patients for the best therapy should not rely on viability assessment alone. When deciding for revascularization, other multifactor determinants include; clinical situation, symptoms and co-morbidities such as diabetes mellitus and renal failure that may substantially contribute to mortality in the follow-up period, should be considered. Lack of functional recovery after revascularization is not always associated with poor patient's outcomes. Survival benefit of such patients may possibly result from the impact of revascularization in other factors that prevent further infarction and death [59]. Thus, despite the increased risk of revascularization, preserved viability may suggest a net clinical benefit.

The recent ESC and the European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization, and the current ACC/AHA guidelines on heart failure advice that the detection of viability should be included in the diagnostic work up of patients with CAD and severe ventricular dysfunction [60–62].

6. Conclusion

Non-invasive myocardial imaging plays a pivotal role in the evaluation of viable myocardium in patients with CAD and LV dysfunction since the presence and extent of viable myocardium have become a valuable clinical strategy for determining the need for revascularization and predict the improvement in patient's clinical outcome regarding LV function recovery, symptoms and survival.

The tables below summarize the most recent available data that shows high sensitivity for the assessment of myocardial viability for both non-invasive myocardial perfusion and function modalities. However, there is a wide range of specificity varying from 38% up to 91%. Direct comparisons between radionuclide imaging and CMR imaging techniques and dobutamine stress echocardiography in the same patients are limited. The recommended approach to assess myocardial viability begins with either functional images in the form of DSE and Dobutamine stress CMR imaging or perfusion images in the form of radionuclide myocardial perfusion imaging (SPECT) and LEG-CMR, depending on availability and local expertise. Furthermore, PET scanning has a greater sensitivity and is a good alternative, however PET, CMR and MDCT may be more challenging to perform and not as widely available. Further studies are needed to determine the incremental values of MDCT perfusion images.

Myocardial perfusion images	Sensitivity	Specificity	PPV	NPV
MCE [28]	82%	74%	…….	……..
SPECT thallium-201 imaging [12]	87%	54%	67%	79%
SPECT Tech-99 m Sestamibi [12]	83%	65%	74%	76%
PET [12]	92%	63%	74%	87%
LGE-CMR [15]	95%	51%	69%	90%
MSCT (ED vs LE) [47]	57% vs 73%	90% vs 85%	…….	……..

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Myocardial function images	Sensitivity	Specificity	PPV	NPV
EDWT-ECHO [13]	94%	48%	53%	93%
EDWT-CMR [15]	96%	38%	71%	85%
DSE [12]	81%	78%	75%	83%
DSE-SRI [17]	83%	84%	....	....
Adenosin-SRI [18]	83.9%	81.4%	....	....
Dobutamine stress CMR [15]	81%	91%	93%	75%

NPV = negative predictive value; PPV = positive predictive value; MCE = Myocardial contrast echocardiography; SPECT = Single-photon emission computed tomography; PET = Positron Emission Tomography; LGE-CMR = Late-gadolinium enhancement CMR; MSCT = Multi slice CT; ED = Early perfusion defects; LE = Late enhancement; EDWT = End diastolic wall thickness; DSE-SRI = Dobutamine stress echocardiography-Strain rate images.

Finally, both myocardial perfusion and function based imaging modalities provide complementary information about myocardial viability in CAD patients and at present, no sole test has evolved to provide all the necessary diagnostic tools with acceptable access, cost, and safety in a single package.

Conflict of interest

None.

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