

Predictive Value of Index of Microcirculatory Resistance (IMR) For Recovery of Left Ventricular Functions in Patients of Acute Myocardial Infarction Undergoing Delayed PCI.

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ABSTRACT

Background: Index of microcirculatory resistance (IMR) has been correlated with recovery of left ventricular function has been extensively studied in patients of acute ST elevation myocardial infarctions undergoing primary percutaneous intervention (PCI) within 12 hrs of chest pain but its st in patients undergoing delayed revascularisation is unclear/ not addressed. **Methods & Results:** Twenty-two patients admitted with ST-elevation myocardial infarction of >12 hrs-21 day duration were enrolled in the study. Coronary flow reserve (CFR), post procedure TMPG grade and index of micro vascular resistance (IMR) measured immediately post stent placement. Basal Infarct size and left ventricular ejection fraction (LVEF) were assessed either before or within 24 hour of PCI and then at 4-months follow-up study. There was a highly significant inverse correlation between IMR measured at baseline and recovery of left ventricular ejection fraction at 4 months ($r = -0.8$, $p < 0.001$). None of the other variables like Post procedure TMP grade, CFR, baseline ejection fraction or baseline infarct size had any correlation with recovery of left ventricular ejection fraction or with changes in infarct size. There was a significant inverse correlation between IMR value and time delay in reperfusion therapy ($r = -0.489$, $p = 0.02$). **Conclusion:** we concluded that also in patients undergoing delayed reperfusion therapy, intra procedural IMR value correlates strongly with recovery of left ventricular ejection fraction.

Keywords: Acute Myocardial Infarction, Microcirculatory Resistance, Left Ventricular Function, .

INTRODUCTION

Primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction is an established reperfusion strategy.^[1] Myocardial function recovery relates to time to reperfusion, with delayed reperfusion resulting in increased micro vascular damage and decreased recovery of function. In real world practice however several patients reach late and have delayed PCI anytime beyond 12 hour to several days post MI,^[3] and not all have been seen to have poor outcomes.^[17] The magnitude of myocardial damage in post AMI patients varies from case to case, irrespective of time delay since chest pain, which primarily determines the recovery of left ventricular ejection fraction in patients undergoing PCI at varying time intervals. Despite achieving normal epicardial coronary artery flow post revascularisation, a significant proportion of patients have a poor outcome possibly because of micro vascular coronary damage.^[3,4] The aim of current treatment for acute MI is to obtain reperfusion, not only at the level of the epicardial artery but also at the tissue level which would indirectly help in

recovery of impaired left ventricular ejection fraction.^[16] A reliable test which can differentiate between recoverable and non recoverable patients has not been fully elucidated. Recently, a novel measure, the index of microcirculatory resistance (IMR) was proposed and validated for assessing the status of micro circulation in patients undergoing primary PCI within 12 hour to predict recovery of left ventricular function.^[5] The index of microcirculatory resistance (IMR) is a new measure of micro vasculature function using a pressure sensor/thermistor-tipped guidewire. IMR has been validated in animal models and also tested in stable coronary artery disease patients.^[5-10] The potential advantages of IMR over current methods for evaluating the microcirculation are its relative ease of performance and interpretation, its quantitative nature, its independence of the epicardial vessel stenosis, and its reproducibility.

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There is no study however, evaluating the role of IMR as a predictor of left ventricular function recovery in MI patient who are undergoing delayed reperfusion therapy beyond 12 hours to several days. Thus the goal of this study was to evaluate the value of IMR obtained during PCI in STEMI patients receiving delayed reperfusion i.e ≥ 12 hour to < 21 days, as a predictor of extent of myocardial damage and predicting left ventricular recovery of function at 4 months follow up.

MATERIALS AND METHODS

Patients

Consecutive patients of acute myocardial infarction patients admitted in our institution between April 2011 and October 2011 and being taken for percutaneous coronary intervention (PCI) with stenting more than 12 hour but within 21 days of onset of symptoms were enrolled in this study unless they met the exclusion criteria as under.

Exclusion criteria

- Age < 18 or > 75 years
- Chronic kidney disease, serum creatinine > 3.0 mg/dl
- Cardiogenic shock,
- Prior MI,
- Previous coronary bypass grafting,
- Culprit lesion located in distal coronary artery
- Significant arrhythmia rendering an invasive coronary physiological study inappropriate.

Informed consent was obtained from each patient before the procedure and the study protocol was approved by the Ethics Committee of our institution. At admission, all patients were pretreated with aspirin (300 mg) and clopidogrel (600 mg) or prasugrel (60mg) orally and an intravenous bolus of 5000 i.u of heparin was administered at the time of sheath insertion to attain an ACT of 300 s. PCI was performed routinely through Right radial artery according to standard clinical practice for percutaneous intervention and stent implantation. Patients received conventional drug therapy according to individual needs, which was determined by the attending physician. Patients who underwent stent implantation received maintenance anti-platelet treatment with clopidogrel 75 mg/day or prasugrel 10 mg daily and aspirin 150 mg/day regimen. All cineangiograms were reviewed and analysed with a computer-assisted, automated edge-detection algorithm (Seimens Medical System,) using standard quantitative definitions and measurements. Thrombolysis in Myocardial Infarction (TIMI) flow grade and TIMI myocardial perfusion grade (TMPG) were evaluated using a scale of 0 – 3 from the final coronary angiogram after PCI. Collateral flow was graded according to the Rentrop classification of 0-3 from the initial coronary angiogram.^[11]

Measurement of IMR (Index of Microcirculatory Resistance)

After successful stenting of the culprit vessel, a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) was calibrated outside the body, the pressure equalized to the guiding catheter pressure with the sensor positioned at the ostium of the guiding catheter, and then advanced to a point distal to the culprit lesion, in distal coronary bed. IMR is defined as simultaneously measured distal coronary pressure divided by the inverse of the thermodilution-derived hyperaemic mean transit time (hT mn), or more simply, distal coronary pressure multiplied by the hT mn [mmHg s or units (U)] both at rest and during hyperaemia by methods described previously.^[11,12] The mean transit time of room temperature saline injected down the coronary artery was determined using a thermodilution technique.^[13] Briefly, with commercially available software (Radi Medical Systems), the shaft of the pressure wire can act as the proximal thermistor by detecting changes in temperature-dependent electrical resistance. The sensor near the tip of the wire simultaneously measures pressure and temperature and can thereby act as a distal thermistor.

Three injections of normal saline, 3 ml each, at room temperature were injected into the coronary artery and a baseline mean transit time (bTmn) was measured. Intra-venous adenosine (140 mc g/kg/min) was then administered to induce steady-state maximal hyperaemia and three more injections of saline 3 mL each at room temperature were given, and the hT mn was measured. Simultaneous measurements of mean distal coronary pressure (Pd), were also made in the resting and maximal hyperaemic states. An average of the three values was provided by the machine as the mean hyperaemic transit time (hTmin).

The distance from the ostium of the vessel to the position of the pressure sensor in double vessel was measured and recorded at the end of procedure by fastening the torque device to the wire at the hub of the Y-connector with the wire still down the vessel and then measuring the amount of wire pulled out of the catheter to position the pressure sensor at the ostium of the vessel. Knowing the distance may be important, given that the mean transit time could be affected by large differences in sensor distance. Coronary flow reserve, fraction flow reserve, mean transit time (basal and hyperaemia) were measured and recorded. The Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade (TMPG) was assessed from the final recorded Cine images after completion of the procedure and was analysed by experienced observer who was blinded to IMR results. The duration of cine filming was prolonged to at least 3 cardiac cycles to make sure that the entire washout of dye and superimposition of territories was avoided. There was no significant

collateral flow after revascularisation of infarcted territory.

Base line and follow up measurement of LV function

Basal left ventricular ejection fraction in Initial 8 patients was calculated using MUGA study for left ventricular ejection fraction(LVEF) where as in following 14 patients MIBI study was done for estimation of left ventricular ejection fraction and viability was assessed in addition .The same sets of investigation and protocols were repeated at 4 months follow up study ,i.e MUGA/MIBI respectively in respective patients as done in basal study . Accurate estimation of left ventricular ejection fraction was done with MUGA/ MIBI. The added possibility to get both ejection fraction and viability in one study was the reason for change to MIBI score in later cases.

Measurement of infarct size and viability

Resting technetium-99m sestamibi SPECT studies were performed within 24 hour after PCI (n =14) and follow-up was done at 4 months (n=14). All patients received an intravenous injection of 555 MBq technetium-99m sestamibi. SPECT acquisitions were performed 30 minutes after tracer application with a double-head camera system (GE INFINIA HAWKEYE) equipped with dual head gamma camera and 4 slice low dose CT installed on same camera to assess accurate left ventricular ejection fraction and viability . SPECT images were analysed by Bull’s eye quantitative program to evaluate the Infarct size changes between the baselines and follow-up studies. Each polar map was normalized to its own maximal value. The size of defect was calculated with the use of a threshold of 50% as derived from phantom studies and was quantified as percentage of left ventricle. Viability assessment was done in 14 patients during basal study and change in viability at follow up study was also analysed.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The data are shown as mean values, SD for the continuous variables (or median) and as absolute or relative frequencies for categorical variables. The means of Continuous variables were compared using Student’s t-test. Pearson’s correlation analysis test was used to examine the relationship of IMR to recovery of left ventricular function and infarct size.

RESULTS

The study population consisted of 19 men and 3 women with a mean age of 54.8 ± 9.3 years. The mean time from the onset of symptoms to coronary reperfusion was 5.96 ± 5.5 days. All Twenty-two patients enrolled in the study underwent successful angioplasty and accurate thermo dilution mean

transit time measurements were obtained. The mean IMR was 36.5±21.2 U with a median value of 27.6 U. The culprit vessel was the left anterior descending in 16 cases, the right coronary in 3 cases, and the left circumflex in 3 cases. The average distance of the pressure sensor down the vessel was 8.9 ± 1.5 cm. The mean duration of follow up was 120 ±12 days.

Ejection fraction and infarct size at baseline and follow up:

The basal left ventricular ejection fraction as calculated with MUGA/MIBI at the time of presentation of STEMI was 43.3± 13.3 %. At approximately 4 months follow-up, the left ventricular ejection fraction had improved to 48.4± 14.7 %. Thus there was change in ejection fraction of 5.1 ±7.02 %. The baseline infarct size of the total score subjected by the artery in question assessed as perfusion defect on MIBI scan was available in 14 patients, and was 37.9±20.8 % at baseline and 32.3±23.8 %at 4 month follow up. There was decrease in defect size on MIBI by 5.0± 9.01 %.

Relation between IMR and left ventricular recovery parameters:

There was significant correlation between IMR measured at baseline and recovery of left ventricular ejection fraction at 4 months (r =-0.8, p<0.001,[Figure 1]). On multivariate analysis index of microcirculatory resistance (IMR) was only independent predictor of recovery of left ventricular ejection fraction (P= 0.049).

There was no significant correlation between IMR and basal infarct size (n=14), or infarct size measured at 4 months follow up. CFR, Post procedure TIMI flow grade, baseline ejection fraction and baseline perfusion defect on MIBI had no significant correlation with improvement in ejection fraction. [Table 1].

IMR and time delay of procedures.

There was weak inverse correlation between IMR and time delay of PCI with respect to time to symptom onset (r = -0.489, p =0.022).The time delay in procedure also correlated weakly with recovery LV function at follow up also (p=0.02,[Figure 2]).

Table 1: Showing correlation of different clinical variable with recovery of LV function. Variable marked with (*) identifies as independent predictor of recovery of LV function on multivariate analysis.

Predictors of recovery of left ventricular function		
Clinical variables	Correlation coefficient(r value)	P value
IMR*	-0.8	P<0.001
CFR	-0.045	P=ns
Post procedure TMPG	0.345	P=ns
Basal EF	-0.007	P=ns
Infarct size(Basal perfusion defect on MIBI)	-0.18	P=ns
Time duration(symptom to procedure)	0.489	P=0.02
Fasting blood sugar	-0.534	P=0.02

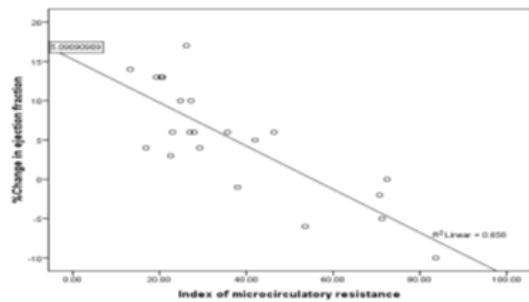


Figure 1: Scatter diagram showing relation between IMR and recovery of LV FUNCTION

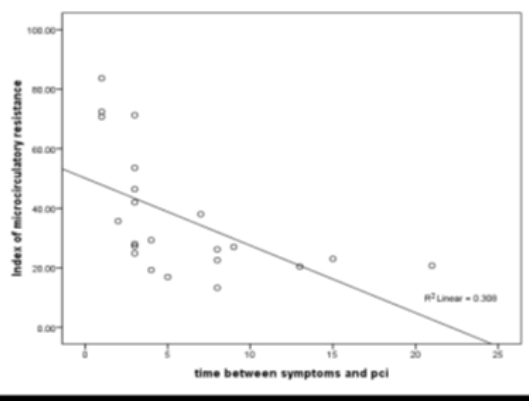


Figure 2: Scatter plot of IMR and time since occurrence of MI in days.

DISCUSSION

Primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction is an established reperfusion strategy and PCI has been known to improve clinical outcomes in patients with acute myocardial infarction MI.^[1,2] However, micro vascular perfusion is often impaired after primary PCI, and reperfusion of the epicardial coronary artery will not always guarantee reperfusion at the myocardial tissue level. Micro vascular injury is determinant of left ventricular function and prognosis after acute myocardial infarction. Fearon et al showed that the index of microcirculatory resistance (IMR), derived from the principle of thermo dilution using coronary dual sensor guide wires using temperature and pressure sensor, was an independent predictor of myocardial function recovery in patients undergoing reperfusion therapy of the IRA within 12 hour of acute myocardial infarction.^[5,13]

In real world practice, however there have been several patients with acute myocardial infarction who reach late and have delayed PCI procedures and not all of the patients do equally bad meaning thereby several of them do well either. We in this study calculated IMR in real world patients undergoing delay reperfusion therapy (>12 hour of chest pain and up to 3 weeks of MI) using a coronary pressure wire as an on-site quantitative

measure of micro vascular function and left ventricular function recovery after PCI. The study was designed to assess the usefulness of IMR for predicting LV function recovery and reduction in infarct size. Our major observation is that IMR proved to be a useful table measure for predicting recovery of LV function at 4 month follow-up in patients with AMI having delayed PCI. Further IMR stood out as only independent predictor of recovery of LV function on multivariate analysis among all other variables including CFR /TIMI flow grade or myocardial perfusion grade post procedure, and basal EF. It however could not correlate with basal infarct size possibly due to small number of patients and may be a much wide variation in infarct size in the study cohort because of the wide time interval of inclusion of cases from > 12 hrs to 21 day post MI.

In published studies of IMR in acute STEMI, the median value of IMR was 32 and in stable coronary artery it was 22 with cut off value of 33 for recovery of left ventricular function primary PCI cases revascularised within 12 hour.^[14,15,18] The median value of IMR in our study was 27.6 which is in-between the value derived in primary PCI patients and those with stable coronary artery disease patients. With several of the delayed patients getting closer to stable to disease by virtue of time and several sicker ones being natural survivors having possible lesser microvascular damage. Our study however certainly shows that IMR has an equal predictive accuracy to recovery of left ventricular ejection fraction on these patients undergoing delayed PCI post-acute MI just as patients undergoing early primary PCI. We, however could not determine cut off value of IMR for left ventricular function recovery predication in our study because of somewhat lesser number of patients than those in acute AMI study groups.

There was significant inverse correlation between IMR and time to reperfusion suggesting that those patients who were intervened later had lower IMR values than those who intervened earlier and this could be explained by the natural cooling down of the patients with time being natural survivors. This in a way suggests that if PCI is delayed beyond the recommended 12 hour for any reason, it is probably better to intervene later in a cooled off patient rather than early say 12 -48 hour, when the left ventricle is more oedematous and there is high IMR, possibly results in poorer risk benefit ratio. Further, because the IMR is measured post revascularisation its utility in prospectively selecting patients who benefit from PCI in these late presenting cases may remain unclear.

CONCLUSION

Index of microcirculatory resistance is a good independent predictor for recovery of left ventricular ejection fraction in patients undergoing delayed

reperfusion (>12 hrs up to 3 weeks) just as in patients undergoing primary PCI within 12 hrs of chest pain.

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