Analysis of Soluble Factors During Percutaneous Coronary Intervention in ST Elevated MI

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Abstract

Aims/Objective

To analyze soluble thrombotic and inflammatory factors responsible for reperfusion injury followed by PCI in patients of ST elevated Myocardial Infarction (STEMI).

Material and Methods

Ten patients with STEMI who were also thrombolysed and came for routine PCI from 24 hours and after were recruited in the study. Peripheral and coronary sinus blood samples before angioplasty, after balloon dilatation, after stenting and a peripheral blood sample at 24 hours were collected successfully for 6 patients out of 10 recruited. The components analyzed were sCD40L, P-selectin, MCP-1, MMP-9, CKMB and Troponin I.

Results

There was not much variation in the components analysed in the peripheral and coronary blood samples before angioplasty, after balloon dilatation and after stenting. However, in peripheral blood sample at 24 hours significant increase ($p<0.05$) in soluble (s) CD40L, MCP-1, MMP-9, and sP-Selectin was observed as compared to the peripheral samples before angioplasty.

Conclusion

The present study demonstrated elevated levels at 24 hours of increased soluble inflammatory and thrombotic components following reperfusion by intervention. Modulation of these components may protect the heart from reperfusion injury over and above the conventional management of reperfusion injury for insoluble particulate matter.

Keywords: Reperfusion Injury; Coronary interventions; Acute Myocardial Infarction

Introduction

Currently, early and successful myocardial reperfusion after an ST elevated myocardial infarction (STEMI) with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcomes. However, there is dissociation between coronary angiographic patency observed and the salvaged myocardium. This led the researcher's to believe that the process of reperfusion although beneficial in terms of myocardial salvage may come at a cost owing to a process known as Reperfusion Injury (RI).

Reperfusion has been referred by Braunwald and Kloner [1] as the "Double edged sword" because reperfusion itself may lead to accelerated and additional myocardial injury beyond that generated by ischaemia alone. This implies that optimization of reperfusion therapy could further improve acute myocardial infarction (AMI) management by salvaging myocardium lost due to RI.

Distal embolization of atherothrombotic debris has been increasingly recognized over the past years as an important mechanism contributing to microcirculatory impairment. This atherothrombotic material has both insoluble (particulate) and non-particulate (soluble) matter which may be responsible for increasing the microvascular damage. Thrombo aspiration devices and distal protection devices have been used for retrieval of atherothrombotic debris, which would have otherwise embolized into the microcirculation [2]. The clinical benefits of such devices in primary PCI have remained inconclusive despite the capture of insoluble atheromatous material, and the largest trials to date were strikingly neutral, with no evidence of benefit or harm [3,4]. Salloum et al. [5] during PCI of Saphenous Vein Grafts had demonstrated that in spite of using distal protection devices i.e. filters to capture the insoluble particulate matter, there were soluble factors which may injure the distal microvascular bed. This may explain the additional myocardial injury occurring post reperfusion therapy. The presence of soluble factors during PCI in coronary and peripheral levels are current interest of many investigators and are studied in detail and targeted to optimize maximal myocardial salvage. Thus, in the present study the aim was to analyse the atherothrombotic non-particulate (soluble) matter which may be responsible for reperfusion injury after PCI.

Reperfusion injury of the myocardium may be viewed multifactorial responses of the vascular tissue to balloon, reflow and stent injury which include disorders of electrolytes, endothelial dysfunction, platelet activation, and clotting-plasminogen imbalance [6-8].

CD40 Ligand (CD40L) is a trimeric, transmembrane protein present in platelets and together with its receptor CD40, is an important contributor to the inflammatory processes that lead to coronary thrombosis [9]. It is found to be increased on platelets in fresh thrombus [9]. This pro-inflammatory substance is released from activated platelets as soluble CD40 ligand (sCD40L) [10]. The present study therefore, aimed at analyzing sCD40L a soluble factor related to platelet activation during PCI. Further it is reported that on endothelial cells or monocytes, the engagement of CD40 leads to the synthesis of other inflammatory factors such as cell adhesion molecules (CAMs), chemokines, and activation of matrix metalloproteinases (MMPs) [10]. Thus levels of P-selectin; another marker of platelet activation as well as a cell adhesion molecule, monocyte chemoatractant protein-1 (MCP-1) and matrixmetalloportienase -9 (MMP-9) were also analysed in patients of ST elevated MI followed by angioplasty in peripheral as well as coronary sinus samples withdrawn before, after balloon angioplasty and after coronary stenting. These factors can potentially mediate in situ inflammation and thrombotic response, which may aggravate the RI.

Materials and Methods

This study was performed at Sir H N Hospital and Research Centre, Mumbai. The subjects were recruited in study only after obtaining their informed consent.

Study Population

Ten patients within the age limit of 30-70 years, with chest pain and STEMI who came to the tertiary centre for routine PCI from 24 hours and after were recruited in the study. These patients had no history of prior MI and had single vessel disease (SVD) which was totally occluded or showing a

thrombus burden on angiography. Out of 6 patients 5 were having TIMI I flow while one had TIMI III. All patients were thrombolysed and further received 325mg Aspirin, 300mg Clopidogrel followed by 75mg Clopidogrel with ACE inhibitors, beta blockers and statins. The exclusion criteria of subjects was prior MI, acute pulmonary edema or cardiogenic shock, arrythmias, renal failure, hepatic dysfunction, multi-vessel disease, occluded LAD which could not be opened or any other documented terminal illness.

PCI and Coronary Sinus (CS) Sampling

All patients underwent angiography followed by balloon angioplasty and stenting via femoral artery with standard technique. Systemic anticoagulation for the procedure was given with unfractionated heparin. All patients received intracoronary nitroglycerine and Nicorandil following balloon dilatation and stenting. CS cannulation was done by experienced electrophysiologist with St Jude CS catheters and Swan Ganz balloon catheter which was kept in the CS. During coronary balloon dilatation and coronary stenting the CS was not occluded. However, it was occluded by the Swan Ganz balloon as soon as coronary artery balloon was deflated subsequent to balloon angioplasty and stenting so as to collect the immediate blood samples after the balloon dilatation and stenting. Ten ml of blood sample was collected from peripheral vein and CS at three different points of time, prior to angioplasty (P1 and C1 respectively), immediately after coronary balloon dilatation (P2 and C2 respectively) and immediately after coronary stenting (P3 and C3 respectively). One more peripheral blood sample was collected at 24 hours (P4) after the procedure. This study was approved by the scientific and ethical committee of the institution.

At the conclusion of the procedure, patients were admitted in intensive cardiac care unit (ICCU) for observation. Standard post-stent therapy comprising of enteric coated Aspirin 150mg, Clopidogrel 150mg, ACE inhibitors, metoprolol and statins were given till discharge. A 12-lead electrocardiogram was routinely recorded immediately and the morning after the procedure. Clinical follow-up was conducted every 15 days up to three months by the referring physicians and the information was gathered prospectively from the patients' medical records. Clinical parameters included recurrent treatment, myocardial infarction, emergent or need for target vessel revascularization and death.

Analysis of Soluble Components

Blood samples were collected and centrifuged immediately. Serum or plasma was stored at -80°C until the time of assay. Analysis of sCD40L, MCP-1, MMP -9 and P-selectin was carried out by enzyme linked immune sorbent assay (ELISA) from R and D Systems, (R and D Systems Inc. Minneaolis Inc. Minneaolis). Components of Myocardial Injury: CK-MB (Erba) and Troponin I (Minividas) were also analysed.

Statistical Analysis

Parametric variables were expressed as Mean ± SD and non-parametric variable were expressed as median with inter quartile ranges. Non-parametric test such as Wilcoxon Signed Rank test was applied to compare significance between two medians of different collection points of same group. A p-value <0.05 was considered statistically significant. Analyses was performed using statistical software SPSS (version 21.0, Chicago, IL).

Results

Four patients were excluded because of inadequate blood sampling from the coronary sinus catheter and the Swan Ganz balloon catheter at the time of PCI. In these four patients we were unable to aspirate full 10.0ml of blood on deflating the Swan Ganz balloon catheter following balloon dilatation and stenting of the coronary artery. The tip of the coronary sinus catheter would collapse on applying negative pressure while aspirating the blood from it. Hence we were left with only six patients in whom we had adequate blood collected from the coronary sinus for analysis. Table 1 shows the demographic, comorbidities, angiography and angioplasty data of remaining six patients. Figures 1, 2, 3 and 4 depict the trend of the coronary and peripheral soluble levels of each patient for sCD40L, sP-selectin, MCP-1 and MMP -9 respectively. The coronary or peripheral blood samples collected before, during and immediately after angioplasty of these six patients for all parameters analyzed did not show any significant trend and there was no significant difference observed between any blood sample collection points (Table 2,3).

At 24 hours, peripheral blood sample of all patients demonstrated increasing trend for CD40L and MCP-1. Increasing trend at 24 hours of peripheral blood sample was also shown of sP-selectin and MMP-9 by all patients except patient no. 4 and 8 (Figure 1-4). The medians of peripheral levels (P4) of sCD40L, sP-Selectin, MCP-1, MMP-9 were significantly elevated

by 10.0, 2.26, 5.75 and 7.3 fold (p<0.05) respectively as compared to the start of the procedure levels (P1) (Table 3). There was no significant trend observed for Troponin I and CKMB in the present study (data not shown).

The pre-procedural peripheral levels of CD40L and MCP-1 in all patients and sP-selectin and MMP-9 in four patients were not elevated. Thus, the rise seen at 24 hours of peripheral blood sample and overall increase in median levels as compared to the pre-procedural levels may be attributed to reperfusion injury.

During the follow-up of six months none of the patient had myocardial infarction, or required emergent target vessel revascularization and none were lost due to death. However patient no. 7 and 8 were clinically unstable and were recommended hospitalization and required recurrent treatment. Patient no. 7 demonstrated maximum rise in peripheral levels at 24 hours (P4) for sCD40L (63.04 fold), sPselectin (9.6 fold), MCP-1 (9.98 fold) and MMP-9 (20.8 fold) as compared to pre-procedural levels (P1). While patient no. 8 did not show rise in sP-Selectin and MMP-9 as stated earlier but demonstrated increase in CD40L (2.1 fold) and MCP-1 (7.72 fold) at P24 as compared to the pre-procedural levels (P1) (Figure 1 and 3). There was also 2.31 fold increase in MMP-9 after stenting (C3) as compared to coronary C1 level (Figure 4) in this patient. The pre-procedural peripheral levels of patient no. 8 of CD40L, P-selectin and MMP-9 as compared to others were also high (Figure 1, 2 and 4).

Table 1. Demographic, Angiographic and PCI data

Age	49.3+12.22 years
Male/Female	4/2
Diabetes mellitus	3
Hypertension	1
Thrombolysis	6
Coronary Angiography Data	
Infarct related vessels LAD	6
RCA/LCX	
TIMI Grade Flow before PCI I	5
II	
III	1
Lesion characteristics TYPE C	6
TYPE B	
PTCA	
Drug Eluting Stents	5
Non-drug eluting	
Stents	
Size & Length of Stent	2.91+0.238x19.5+4.46mm
TIMI Grade Flow after PCI	
I	0
II	0
III	6

Soluble Factors	Coronary Sinus Levels		
	C1	C2	C3
sCD40L (pg/ml)	213 (196/242)	235 (225/259)	254 (190/269)
sP-Selectin (ng/ml)	44.1 (36/53)	48 (45.5/55)	47.3 (42.7/54.3)
MCP-1 (pg/ml)	83 (53.3/110)	65 (61/81)	75.5 (49.6/84)
MMP-9 (ng/ml)	268 (166/ 416)	119 (108/ 359)	198 (102/316)

Table No 2: Coronary Sinus Levels of Soluble Factors

Soluble Factors	Peripheral Levels			Peripheral After 24 Hours
	P1	P2	P3	P4
sCD40L (pg/ml)	284 (189/473)	271 (188/438)	265 (210/337)	2871* (535/12351)
sP-Selectin (ng/ml)	42.6 (14.8/67.3)	53 (38/69)	51.7 (45.3/68)	95* (78.6/199)
MCP-1 (pg/ml)	66.2 (57.4/74)	64.5 (55.6/77.6)	67.7 (55.6/74.5)	380* (189/695)
MMP-9 (ng/ml)	140 (98/165)	73 (68.5/178)	102 (72/ 149)	1026* (404/1684)

Table No. 3- Peripheral levels of Soluble Factors
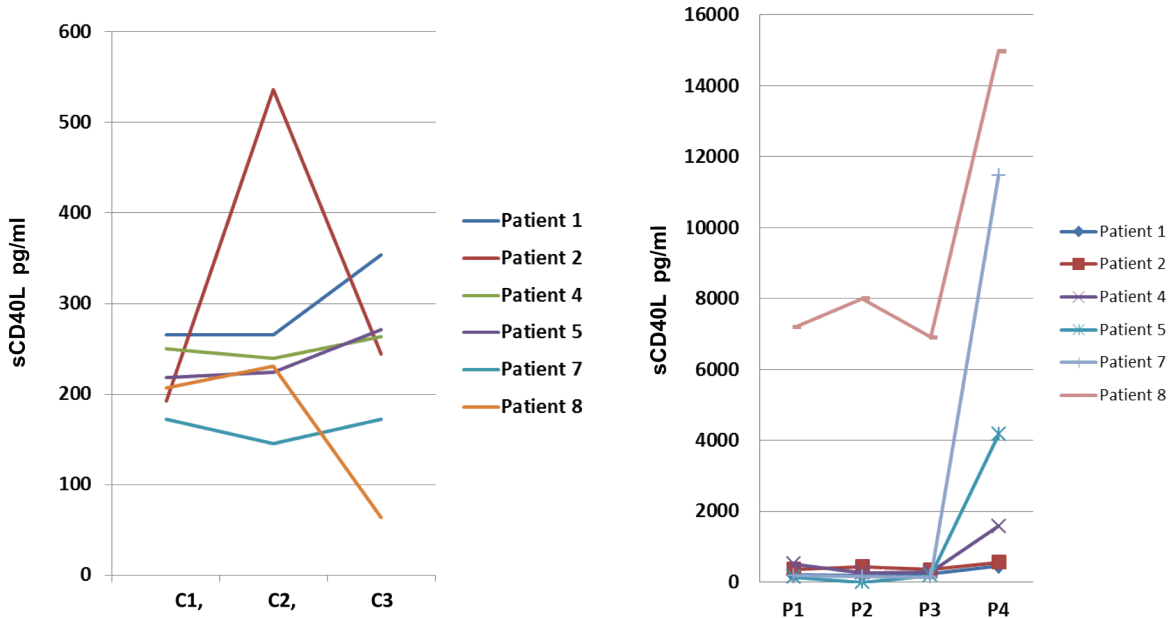
*$p < 0.05$

Figure 1: Soluble levels of CD40L
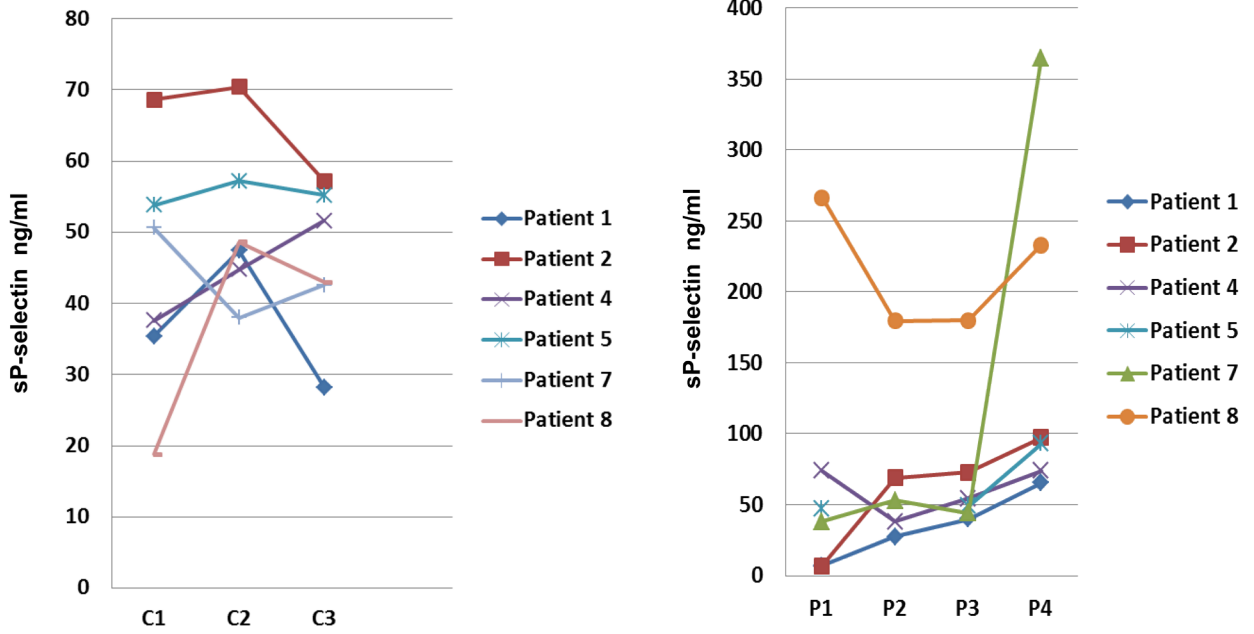
Figure 2: Soluble levels of P-Selectin
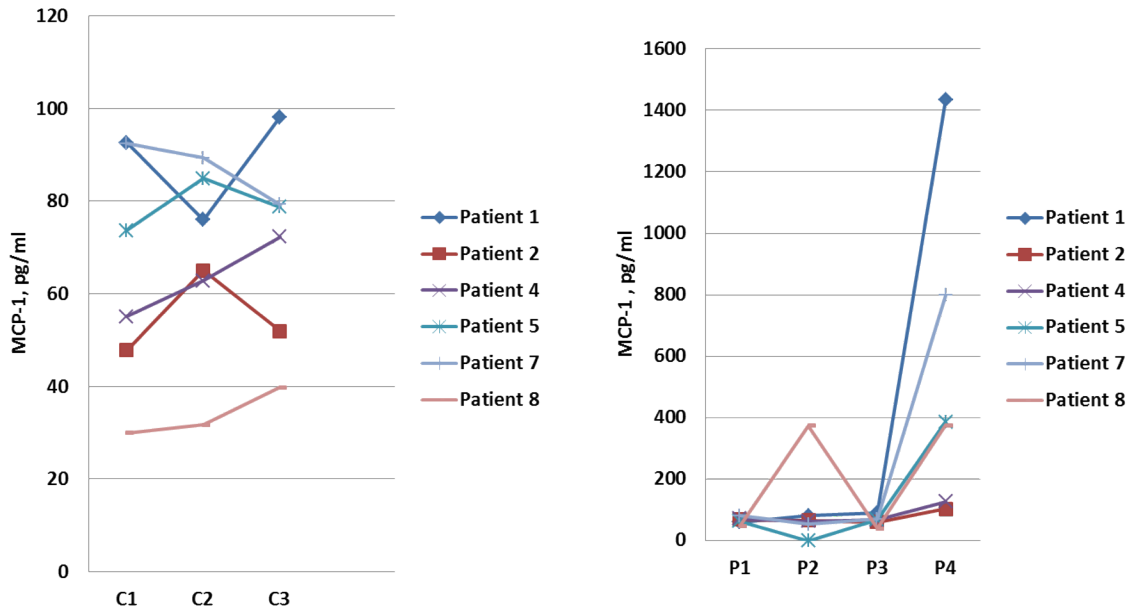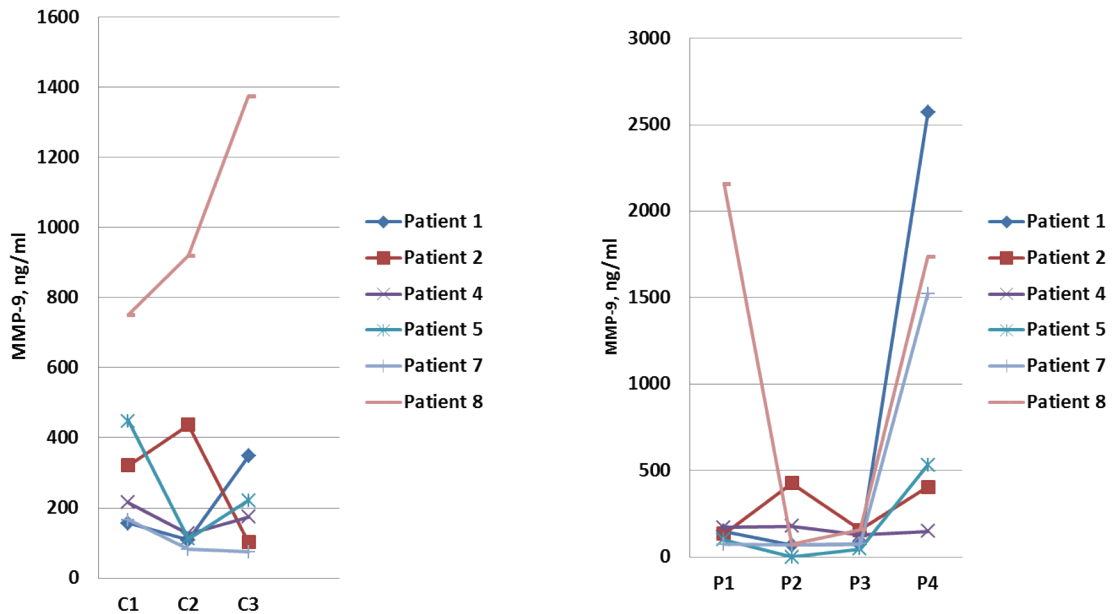

Figure 3: Soluble levels of MCP-1

Figure 4: Soluble levels of MMP-9

Discussion

Balloon angioplasty and stenting results in plaque fracturing that may expose and release various thrombotic, vasoactive and inflammatory components in the distal circulation. In the present study, none of the components demonstrated immediate rise in coronary sinus or peripheral blood samples after ballooning or stenting as compared to the respective blood samples collected just prior to the procedure. However, at 24 hours after PCI peripheral levels of not only sCD40L but also of MCP-1, MMP-9 and sP-selectin demonstrated significant increase as compared to the peripheral levels before PCI. This provides a link between PCI-mediated vascular injury and platelet activation as well as elevation of inflammatory factors.

Salloum et al. [5] in their study of analyzing soluble vasoactive factors during PCI of saphenous vein grafts using the PercuSurge GradWire distal protection devices demonstrated significant increase in sCD40L from the blood sample collected through export catheter immediately after PCI. Ohashi et al. [11] have demonstrated earlier peak of sCD40L in the coronary circulation at 9 hour. Their immunohistochemical study also revealed expression of CD40L on intra-coronary occlusive and mural thrombi and aspiration of the same reduced the increase in both sCD40L and MMP-9 activity. Obradovic et al. [12] in multivariate linear regression analysis adjusted for clinical characteristics and type of pre-intervention therapy demonstrated that at 24 hours increased platelet aggregation was the only independent predictor of sCD40L and sP-Selectin levels.

P-selectin is a cell surface glycoprotein that plays a critical role in the migration of lymphocytes into tissues. It is found constitutively in a preformed state in the Weibel-Palade bodies of endothelial cells and in α-granules of platelets. This stored P-selectin is mobilized to the cells surface within minutes in response to a variety of inflammatory and thrombogenic agents. Thus P-selectin is a marker of platelet activation which in turn is prerequisite

for thrombosis [13]. Increase in sP-selectin have been reported by Yu et al. [14] and by Berns et al. [15] who have further also reported association of increased risk of restenosis on 10th day with elevated sP-Selectin. Contrary to these reports Ratkovic et al. [16] have demonstrated post procedural decrease in sP-selectin levels after emergency PCI.

As stated earlier, sCD40L or sP-selectin levels in the present study did not show immediate rise in coronary circulation or peripheral levels after ballooning or stenting but was elevated in peripheral sample at 24 hours. No increase immediately after PCI of sP-selectin or CD40L level could be due to Nicoranadil treatment as stated by Lee et al. [17] or anti-platelate treatment which may decrease the platelet activation and thus may explain no change in sP-Selectin or sCD40L.

MCP-1 is a chemokine that critically regulate basal and inflammatory leukocyte trafficking and may play a role in angiogenesis [18]. In case control studies plasma MCP-1 concentration has been shown to be associated with restenosis after coronary angioplasty [19]. Increase in MCP-1 levels at 4-6 to 12 hours [20] and further till 30 days [21] after PCI have been reported. Preadmission levels of MCP-1 levels have been demonstrated to be associated with failure of ST resolution and rise of no reflow [22].

Matrix turnover is crucial to tissue repair and matrix metalloproteinases (MMPs) are key enzymes involved in matrix degradation. MMP-9 is one of the MMPs expressed in the heart [23]. Increased myocardial MMP-9 expression or activity has been found in a variety of experimental myocardial injuries such as the permanent coronary artery occlusion model in the RI model in porcine [24]. Rise in MMP-9 level have been reported by Robertson et al [25] and Higo et al [26] immediately after PCI in coronary circulation but not at systemic level [25]. In the present study MMP-9 levels did not vary immediately after PCI from before but demonstrated rise in the peripheral levels at 24 hours. Similar findings have been reported by Liu et al

[27], Hedstrome et al [28], Inoue et al [29] and Dai et al [30]. While Fernes et al [31] have reported significant decrease in MMP-9 levels at 24 hours. Delay in the rise of MMP-9 till second day was correlated to Niocorandil by Fujiwara et al [32] which could also be the reason of no variation in MMP-9 levels observed during or after PCI in the present study.

Ying et al [33] however have reported 28.8% increase in sP-Selectin in blood sample collected 5 minutes after PCI and significant correlation with inflation pressure. They have further stated that patients with elevated sP-selectin levels at 24 hours required recurrent treatment at six month follow-up. In the present study, of the two patients who required recurrent treatment, one patient was associated with elevated peripheral levels of all the inflammatory markers at 24 hours and second had increased pre-procedural peripheral levels of sCD40L, sP-Selectin and MMP-9 and significant increase in peripheral levels at 24 hours of sCD40L and MCP-1.

Thus present study was undertaken with the aim of identifying the pathogenic components of thrombotic plaque in the coronary sinus and peripheral blood which may aggravate reperfusion injury. We started with sample size of 10 patients but had to confine analysis of the components of only 6 patients due to non-availability of coronary sinus samples at C2 or C3 levels. From these six patients we were able to identify sCD40L and MCP-1 to be elevated at 24 hours in the peripheral levels in all patients with median increase even in MMP-9 and sP-Selectin. Future therapeutic targeting these parameters may also help in decreasing inflammation and chances of reperfusion injury.

Conclusion

Increased soluble inflammatory and thrombotic components contributing to acute myocardial injury infarction following ischemia–reperfusion, is unexplored. The present study demonstrated elevated peripheral levels of sP-Selectin, MCP-1 and MMP-9 levels along with sCD40L at 24 hours after PCI. Such information will have a significant impact on the understanding of the basic biology of acute myocardial injury, as well as on potential avenues for pharmacological approaches to the treatment on RI. A larger detailed study may help us in modulation of these components which may constitute a potential pharmacological target to protect the heart from RI over and above the conventional management of RI for insoluble particulate matter.

Acknowledgement

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