The role of inflammation in percutaneous coronary intervention, from balloon angioplasty to drug eluting stents

Short title: The role of inflammation in coronary angioplasty

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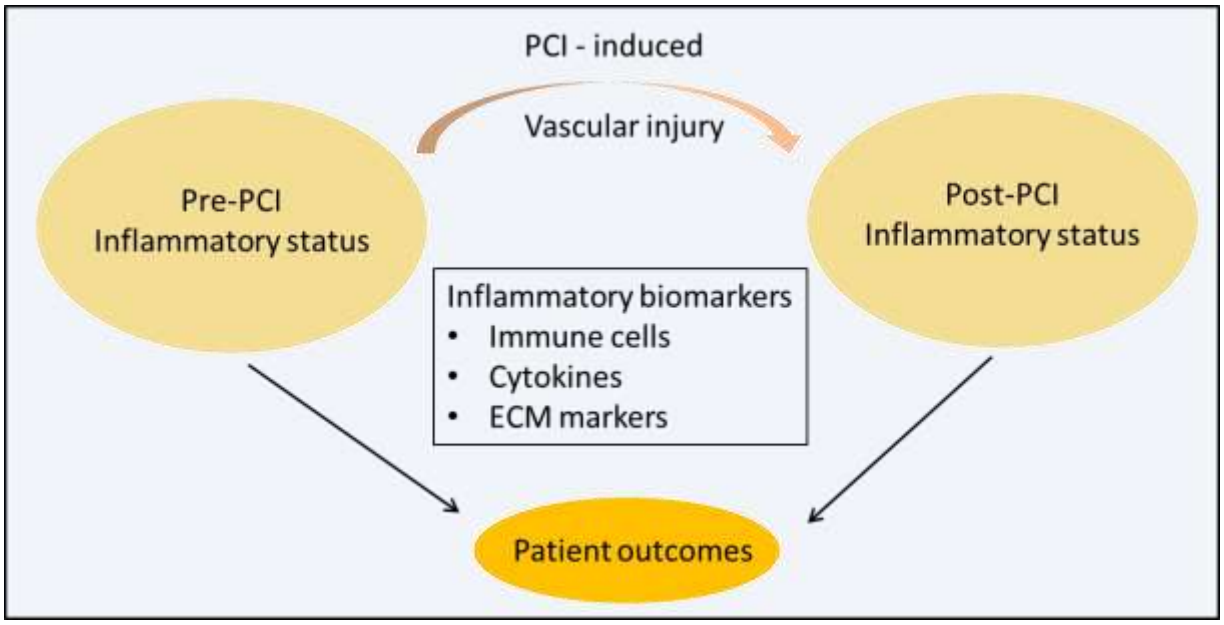
Abstract

The role of inflammation in percutaneous coronary intervention (PCI) has been investigated in numerous studies. Both pre- PCI and post- PCI inflammatory status have been demonstrated to be linked with patient outcomes. C-reactive protein (CRP) continues to be the most studied inflammatory biomarker, while a growing number of additional biomarkers, including cytokines and immune cells, are being assessed. As insights are gained into the complexities of the inflammatory response to PCI, it becomes evident that a targeted approach is necessary to ensure optimal patient outcomes. Here, we review the biomarkers that can predict patient outcomes following PCI and specifically how they differ for balloon angioplasty, bare metal stents and drug eluting stents. A specific focus is given to human studies and peri-procedural inflammation rather than inflammation associated with myocardial infarction.

Graphical abstract

The role of inflammation in percutaneous coronary intervention



Introduction

Over the last few decades, it has been demonstrated that inflammation has a central role in all stages of atherosclerosis as well as the sequelae of percutaneous coronary intervention (PCI) (1) (2) (3). A wealth of studies in animal models, supported by data in humans, have identified various cytokines, growth factors and other biomarkers that interact with multiple immune cells during the inflammatory process (4) (5) (6). Circulating monocytes and their tissue counterparts macrophages have gained great interest in recent years as their multifaceted roles in cardiovascular homeostasis and disease become apparent (7). As insights are gained into the complexities of the inflammatory response to PCI, it becomes evident that a targeted approach is necessary to ensure optimal patient outcomes. Here, we will review the pre-PCI inflammatory status as well as the post-PCI inflammatory response and their relationship to patient outcomes. A specific focus is given to human studies and peri-procedural inflammation rather than inflammation associated with myocardial infarction.

Pre-PCI inflammatory status

Balloon angioplasty

Liuzzo *et al*. demonstrated that the magnitude of the inflammatory response [as assessed by IL-6, C-reactive protein (CRP) and serum amyloid A protein] post balloon angioplasty is determined to a greater degree by the individual responsiveness rather than by the type of provocative stimuli (8). They showed that increased baseline levels of inflammation in patients with unstable angina determine hyper responsiveness of the inflammatory system even to small stimuli; while plaque rupture per se is not a major cause of the inflammatory response (8). Pre-procedural levels of CRP and serum amyloid A protein have been demonstrated to be independent predictors of clinical restenosis post balloon angioplasty (9). Immunohistochemical analysis of direct atherectomy samples has associated the extent of

initial coronary plaque inflammation (macrophages and T lymphocytes) with recurrence of unstable angina after direct coronary atherectomy (10). Macrophages in direct coronary atherectomy samples from patients with unstable angina have also been found to be an independent predictor of restenosis (11). Furthermore, the activation status of blood phagocytes (expression of CD66 by granulocytes and production of IL-1β by stimulated monocytes) can independently predict restenosis post balloon angioplasty (12). The data suggest that the systemic, as well as the local levels of inflammation pre-PCI, play significant roles in development of restenosis or adverse patient outcomes after balloon angioplasty (Figures 1 and 2).

Bare metal stents (BMS)

Elevated pre-procedural CRP has been consistently shown in studies to be an independent predictor of death or myocardial infarction after BMS implantation (13) (14) (15). Most studies, including a large meta-analysis of 2747 patients undergoing BMS implantation, have demonstrated that baseline CRP is also an independent risk factor for in-stent restenosis (ISR) (16). Treatment with statins appears to abolish the increased risk conferred by elevated baseline CRP (13) (14). The association between baseline CRP and BMS-ISR, further supports the concept that pre-procedural activation of the inflammatory system can modulate the response of vessel wall to injury (5) (Figures 1 and 3).

Interleukin-3 (IL-3), synthesized by activated T cells in atherosclerotic plaques, can activate smooth muscle cell migration and proliferation and also increase vascular endothelial growth factor production (17). IL-3 can upregulate adhesion molecules such as P selectin and it is considered a mediator of chronic, rather than acute, inflammation(18). Rudolf *et al*. have demonstrated that IL-3 is an independent predictor of ISR after BMS and that patients with

symptomatic stable coronary disease undergoing PCI have higher IL-3 levels than patients with acute coronary syndrome (ACS) who have higher levels than patients with asymptomatic stable coronary disease (18). These findings suggest that IL-3 is possibly stimulated by the duration and extent of myocardial ischaemia (18).

White blood cell (WBC) count is considered a marker of cellular inflammation and it has been demonstrated that it can predict major adverse cardiovascular events (MACE) in the context of ACS(19). Gurm *et al*. studied the relationship between baseline WBC and long-term mortality in 4450 patients with mainly stable and unstable angina being treated mostly with BMS. They demonstrated that WBC was an independent predictor of mortality in this population as well and were the first to demonstrate a J-shaped relationship between WBC and long-term mortality (20).

Drug eluting stents (DES)

The significance of pre-procedural CRP as a predictor of patient outcomes has been consistently demonstrated by multiple studies in DES era (Figures 1 and 4). Park *et al*. showed that baseline CRP was an independent predictor of cardiovascular mortality or MI in a study of more than 1600 patients (predominantly stable and unstable angina) being treated with DES. Baseline CRP did not predict ISR but angiographic follow-up was restricted to 6 months in the study (21). The same group identified baseline CRP as an independent predictor of stent thrombosis as well as death and MI, in their prospective study of more than 2600 stable and unstable angina patients with median follow up of 3.9 years (22). In a study of more than 900 patients undergoing elective DES implantation, baseline CRP was an independent predictor of death or myocardial infarction at 2 year, even though CRP did not predict target vessel revascularisation in that study either (23). However, in a study of 167 patients on hemodialysis undergoing elective DES implantation, baseline CRP was an independent predictor of MACE

and in-stent restenosis (24). Furthermore, Nicolli *et al*. demonstrated in a small study of 92 patients that baseline CRP was associated with a more aggressive (diffuse) ISR pattern after DES implantation (25) . More recently, the long-term prognostic significance of baseline CRP was further evaluated. Oemrawsingh *et al*. demonstrated in more than 400 patients undergoing PCI for stable angina or ACS, that CRP is an independent predictor of mortality or MI after ten years of follow up (26). In conclusion, most of the data demonstrate that pre-procedural CRP is a reliable predictor of hard clinical endpoints including stent thrombosis, with limited value in predicting DES restenosis (27).

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) participates in the oxidative modification of LDL generating pro-inflammatory products. It is secreted by macrophages in the atherosclerotic plaque and considered a biomarker of vascular inflammation (28). It has been shown to be an independent risk marker for coronary artery disease after adjusting for lipid, inflammatory and hemostatic parameters (29). More recently, it was demonstrated that pre-procedural levels of Lp-PLA_2 in patients undergoing elective PCI independently predicted periprocedural myocardial injury (30).

Shah *et al*. have recently demonstrated in their prospective study of >4000 patients (all-comers) that baseline WBC remains an independent predictor of MACE and importantly target lesion revascularisation (TLR) as well, in the modern era of DES and pharmacotherapy. The relationship of pre-PCI WBC and MACE was independent of clinical presentation (ACS vs non-ACS) indicating the importance of baseline cellular inflammation even in the context of stable angina (31).

Inflammatory response to PCI

Thirty years ago, Forrester *et al*. hypothesized that restenosis is a manifestation of the healing response to vascular injury post angioplasty. Platelet aggregation, inflammatory infiltrates,

cytokines, smooth muscle cell proliferation and extra cellular matrix (ECM) were proposed as major components of that healing process(32). Creation of the largest possible residual lumen in combination with substantial inhibition of intimal hyperplasia was thought to be required to resolve restenosis(32).

Balloon angioplasty

Autopsy studies of patients with balloon angioplasty identified smooth muscle cell proliferation leading to intimal hyperplasia as a main component of restenosis alongside the clinically identified vessel recoil. The degree of medial injury was associated with the degree of restenosis while a change in the composition of ECM (from proteoglycans to collagen), was noted at six months(33). A number of biomarkers have been demonstrated to be part of the post-PCI inflammatory response and to predict patient outcomes (Figures 1 and 2). Hojo *et al*. demonstrated that interleukin-6 (IL-6), a multifunctional cytokine with central role in inflammation and tissue injury, increases immediately after angioplasty in coronary sinus and is a predictor of restenosis (34). Increased levels of tumour necrosis factor α (TNFα) and fibronectin (glycoprotein of the extra cellular matrix) have also been demonstrated in atherectomy samples of restenotic lesions post balloon angioplasty (35). Elevated levels of monocyte chemoattractant protein-1 (MCP-1) after elective balloon angioplasty have been shown to be associated with restenosis and to correlate with increased monocyte activity (36) (37). Immunohistochemistry analysis of atherectomy specimens has also shown that restenotic lesions have significantly more macrophages and expression of MCP-1 compared to denovo lesions (38). Taken together these data indicate that macrophages and MCP-1 are implicated in the inflammatory response post-PCI and the development of restenosis. In addition, human studies have implicated that adhesion molecules, important in leucocyte recruitment after vascular injury, play an important role in post-PCI inflammatory response and restenosis.

Balloon angioplasty results in neutrophil activation with upregulation of CD11b and downregulation of L-selectin adhesion molecules (39) (40). Elevated levels of CD11b 48 hours post elective balloon angioplasty have been associated with restenosis and late lumen loss (41) (42). Furthermore, Inoue *et al*. demonstrated that the percentage increase of CD11b in coronary sinus 48 hours post angioplasty was significantly less after cutting balloon compared to standard balloon, providing a mechanistic link between the controlled vascular injury of cutting balloons and less restenosis (42).

Bare metal stents

Bare metal stents provided an effective solution for the acute limitations of balloon angioplasty, such as limiting dissections and acute vessel recoil. The restenosis rate was also improved relative to balloon angioplasty but remained unacceptably as high as 20-30% in the medium to longer term follow up (43). Human autopsy studies from the era of BMS have described the inflammatory response post stent implantation and linked it to ISR. In the initial reparative phase, denudation of the endothelium and plaque disruption following stent implantation leads to thrombus formation, which covers the stent initially. This thin layer of thrombus gradually gets infiltrated by smooth muscle cells (SMCs) and inflammatory cells such as lymphocytes and macrophages. Increased numbers of SMCs accompanied by macrophages and an expansion of the ECM lead to the second proliferative phase (44). Histopathological analysis of directional atherectomy specimens from restenotic lesions has also shown that the cellularity of in-stent neointima decreases over time as proteoglycan-rich ECM increases (45). Morphological, human histology studies further linked arterial injury with inflammation and neointimal growth challenging the concept that ‘bigger is better’(46) (47). Farb *et al*. demonstrated that medial injury or penetration of the stent into a lipid core was associated with

increased chronic inflammation leading to neointimal growth and ISR. Macrophages were one of the most predominant cells of the inflammatory response post stenting(46) (47).

It is established that monocytes, precursors of macrophages circulating in blood, have strategic roles in all stages of atherogenesis with increasing evidence about the great importance of their various subgroups(48). $CD14^{++}CD16^{+}$ (intermediate) monocytes are independently associated with cardiovascular events in patients referred for elective coronary angiography and in non-dialysis chronic kidney disease patients (49) (50). Fakuda *et al*. were the first to identify that the peak monocyte count from peripheral blood, two days after stenting, was the only fraction of leukocytes with significant positive correlation with in-stent neointimal volume at six-month follow-up (51). Their findings demonstrated that monocytes play a central role in the post-PCI inflammatory response (52). Liu *et al*. subsequently demonstrated that the CD14+CD16+CX3CR1+ (intermediate) subset of monocytes 12 days (time point chosen to avoid inflammation from myocardial necrosis) after ST elevation myocardial infarction treated with BMS was an independent predictor for in-stent late lumen loss (53). These limited data indicate that monocytes and most importantly their intermediate subset are closely implicated in the development of BMS-ISR.

A number of inflammatory biomarkers have been shown to increase after PCI with BMS and importantly to be related with patient outcomes (Figures 1 and 3). CRP is an acute-phase protein produced by the hepatocytes in response to stimulation by IL-6 primarily. It has been shown to peak 48 hours post stenting for stable angina while normalisation of CRP at 72 hours post procedure is associated with favourable patient outcomes at 1 year follow up (54). Patients who subsequently develop ISR have significantly higher levels of CRP with a later peak indicating a prolonged inflammatory response, compared to patients without ISR (55). Furthermore, the periprocedural (pre- to 24h-post) change in CRP is an independent predictor of long-term MACE, with additional predictive value when compared to the baseline or post-

PCI CRP value separately (56) (57). Inoue *et al*. have also demonstrated that at least some amount of the CRP post-stenting is produced locally and that CRP production at the site of PCI is associated with Mac-1 activation (58). Mac-1 (CD11b/CD18) is an integrin responsible for firm leukocyte adhesion to platelets and fibrinogen at injured vessels, which has been shown to increase after elective stenting and be a significant predictor of late lumen loss (59). Interleukin-33 (IL-33) is an alarmin mainly expressed by endothelial, epithelial and smooth muscle cells that guides the immune response after cellular injury and enhances cytokine production (TNF-α, IL-6, IL-1β) from macrophages. Data suggest that a decrease in IL-33 levels after stent implantation is associated with lower ISR rate (60). Matrix metalloproteinases (MMPs) have also been linked to the pathogenesis of ISR. MMPs are proteases that control ECM degradation and facilitate intimal remodelling post angioplasty. Increased level of MMP-9 after stent implantation have been shown to be independent predictor of ISR after BMS insertion (61,62).

Drug eluting stents

Drug eluting stents, coated with antiproliferative drugs, were subsequently developed and demonstrated to significantly reduce ISR (43). A human autopsy study from the DES era demonstrated that uneven distribution of drug was associated with ISR while medial injury associated with increased inflammation, angiogenesis and peri-strut haemorrhage was a predictor of DES occlusion. Important differences were identified between DES and BMS restenosis. Even though both BMS and DES had similar macrophage infiltration, macrophage infiltration correlated with neointimal thickness only in BMS but not in DES; indicating suppression of growth factors in DES (63). The neointimal composition of restenotic DES had greater proteoglycan deposition and less smooth muscle cellularity, when compared to BMS which had greater cellularity and collagen deposition (63). However, neointimal area correlated

positively with neointimal vessel and macrophage density but not type of stent, BMS or DES, in another human autopsy study(64). Furthermore, histopathological analysis of directional atherectomy specimens of DES- and BMS-restenotic lesions demonstrated significantly increased macrophages in DES compared to BMS (65). Considering all the studies together, the data suggest that macrophages continue to play a significant role in the pathophysiology of DES-ISR.

Despite the reduction in ISR following the development of newer generation DES, late stent failure continues to be a significant concern following stent implantation. In-stent neoatherosclerosis emerged as an underlying pathophysiological substrate leading to very late stent thrombosis and late ISR. A human autopsy study revealed that in-stent neoatherosclerosis occurs both in BMS and DES, but occurs more frequently and significantly earlier with unstable lesion characteristics in DES compared to BMS (66) (67). Whilst second generation DES have been shown to have significantly less inflammation score compared to first generation DES in autopsy studies, there was no difference in prevalence of neoatherosclerosis and foamy macrophage clusters (68). The exact mechanism leading to neoatherosclerosis remains to be defined; however it has been proposed that the dysfunctional endothelium following stent implantation results in adhesion and migration of monocytes into the sub-endothelium where they convert to foamy macrophages driving the development of the necrotic core to form fibroatheroma (69).

The inflammatory response after coronary stent implantation has been extensively evaluated in the DES era (Figures 1 and 4). CRP is the most-studied biomarker. Dibra *et al*. demonstrated that a more intense inflammatory response following elective PCI, as assessed by CRP measurement, was associated with increased ISR risk only for BMS and not for DES (70). Consistent with these results, Gaspardone *et al*. showed that even though BMS, sirolimus eluting stent (SES), paclitaxel eluting stent (PES) and dexamethasone eluting stent (DEX) elicit

an almost identical systemic inflammatory response as assessed by CRP 48 hours post elective PCI, the SES and PES had a significantly lower ISR (71). Therefore, the lower ISR of DES might be related to a blunted local inflammatory response rather than a decreased systemic inflammatory response. In contrast to these studies, Kim *et al*. showed that BMS elicit more inflammatory response post elective PCI compared to DES as assessed by CRP 48 and 72 hours later (72). Kang et at subsequently demonstrated that PES and SES elicit a similar inflammatory response post elective PCI, as assessed by CRP and IL-6, even though SES had a significantly lower volume of neointimal hyperplasia on intravascular ultrasound (73). Even though this study did not identify CRP or IL-6 as significant predictors of neointimal hyperplasia the follow-up study from the same authors demonstrated a significant positive correlation between CRP level at 24h and 72h post-PCI with neointimal hyperplasia on intravascular ultrasound at 9-month follow up (74). In contrast to the previous studies that measured CRP in the short-term period post-PCI, Hsieh *et al*. measured CRP at 9-month follow up after DES implantation in more than 1700 patients. They showed that elevated CRP 9-months post-PCI is an independent predictor of long-term cardiovascular outcomes including ISR(75). Consistent with these results, Shiba *et al*. in their retrospective study of more than 1200 consecutive patients measured CRP at baseline and 8-12 months post-PCI. They confirmed that late-phase CRP is an independent predictor of MACE including TLR in patients treated with DES (76). The concept of residual inflammatory risk (RIR) post-PCI has been evaluated by two recent large retrospective studies. Kalkman *et al*. first showed in more than 7000 patients (mainly stable or unstable angina) that a persistently high RIR post-PCI (predominantly with DES) was associated with significantly higher all-cause mortality and MI at one year (77). The same group corroborated these results, by demonstrating in more than 3000 patients (included in their previous study) with low baseline cholesterol that persistently high RIR post-PCI

remained an independent predictor of major adverse cardiac and cerebrovascular events at one year (78).

Overall, even though there is some disagreement between the studies, most of the data suggest that all stents elicit a similar systemic inflammatory response, as assessed by CRP, irrespective of type of stent. A local, as opposed to systemic, modulation of the inflammatory response is possibly responsible for the better ISR profile of certain stents. However, a persistently high RIR is an independent predictor of poor patient outcomes post-PCI even in patients with low cholesterol. Post procedural late-phase, rather than short-phase, CRP elevation appears to be a more useful biomarker for the prediction of MACE and ISR in the DES era. Of note though, most of the studies evaluating CRP after DES implantation have included mainly first-generation DES with small number of patients with newer-generation DES (27).

Pentraxin-3 (PTX3), a member of the pentraxin superfamily alongside CRP, has been utilised to assess the local inflammatory response post-PCI. It is produced by macrophages and endothelial cells in response to local inflammation and is highly expressed in the cardiovascular system. There are some data suggesting that BMS have significantly higher levels of PTX3 12 hours after PCI compared to DES; while hsCRP is not significantly different between BMS and DES (79). Haibo *et al*. demonstrated that PTX3 increases significantly 24h after elective DES implantation and that post-PCI PTX3 is an independent predictor of MACE (80). More recently, Kimura *et al*. demonstrated that peak post-PCI PTX3 was associated not only with MACE but also with suboptimal post-stent findings on optical coherence tomography (OCT), linking local inflammation induced by DES implantation with suboptimal stent characteristics and MACE (81).

A variety of pro- and anti-inflammatory cytokines have also been shown to be associated with ISR. IL-18 is a pro-inflammatory cytokine produced by cells participating in the atherosclerotic process such as macrophages, endothelial cells and smooth muscle cells. It plays an important

role in neointimal formation, endothelial cell apoptosis and smooth muscle migration(82). IL-10, a crucial anti-inflammatory cytokine produced by T-helper 2 lymphocytes, macrophages and monocytes, plays critical role in plaque stability(82). Elevated levels of the pro-inflammatory cytokine IL-18 and decreased levels of the anti-inflammatory cytokine IL-10 at baseline, 24h and 2 weeks after PCI have been associated with ISR (82). Furthermore, polymorphisms in IL-18 (-137G/C) and IL-10 (+4259GG) have been associated with ISR(82) (83). IL-35 is an anti-inflammatory cytokine, member of the IL-12 cytokine family with immunosuppressive roles. It inhibits atherosclerotic lesion progression via upregulation of anti-inflammatory cytokines, downregulation of the pro-inflammatory cytokines and decreasing the M1/M2-like macrophage ratio(84). More recently, Liu *et al*. demonstrated that low levels of the pro-inflammatory cytokine IL-1β and high levels of the anti-inflammatory cytokine IL-35 post-PCI, predicted stent strut coverage as assessed by OCT 3 months later (84). The same study also demonstrated that a) in vitro IL-35 induced activation of the anti-inflammatory M2-like macrophage phenotype, which induce endothelial proliferation and alleviate endothelial dysfunction and b) treatment with IL-35 of an in vivo model resulted in lower percentages of uncovered struts and inhibited inflammatory response (84).

Similar to BMS, MMPs have been shown to predict ISR after DES implantation. Increased levels of MMP-2 24h later and MMP-9 24 hours and 2 weeks after elective PCI with DES have been shown to be independent predictors of ISR (85) (82). More recently MMP3 6A6A genotype has been found to be a genetic susceptibility factor for ISR after DES implantation (86).

Therapeutic implications

In summary, PCI induces an inflammatory response via three main mechanisms a) direct endothelial injury b)release of reactive oxygen species (ROS) and c) release of necrotic core

contents (table 1). Both direct endothelial and reperfusion injury induce an inflammatory response with cytokine release, platelet and leucocyte activation. In addition, barotrauma to the plaque causes release of its necrotic core contents. These can provoke further inflammatory response by either distal obstruction or via release of NETs and activation of the NLRP3 inflammasome pathway (6).

Immunomodulation of the pre- and post-PCI inflammatory status has been attempted with variable success over the years. It has long been recognised that statins have a number of beneficial cardiovascular pleiotropic effects, including anti-inflammatory properties (87). Pre-treatment with statins significantly reduces peri-procedural myocardial injury and post-PCI inflammation as assessed by CRP in patients with stable angina (88). In addition, initiation of statin at the time of stent implantation can attenuate the inflammatory response as assessed by CRP 48 hours later and reduce MACE six months later (89). The beneficial effect of statins post-PCI is maintained long-term (90). Colchicine is a potent anti-inflammatory medication that has received much attention following the recent promising results in patients with stable coronary artery disease (not undergoing PCI) and myocardial infarction (91) (92). Few, relatively small, studies have assessed the peri-procedural effect of colchicine, including a mixture of elective and ACS patients. The recent nested inflammatory biomarker sub-study of the COLCHICINE-PCI trial, which included 280 patients with both ACS and stable angina, showed that colchicine attenuated IL-6 and hsCRP increase from baseline to 24h post-PCI (93). Collectively, they show that colchicine attenuates the post-PCI inflammatory response in patients with ACS but not in patients with stable angina (94). It is therefore, unclear if colchicine can reduce PCI-related inflammation or only MI-associated inflammation.

Conclusion

Baseline and post-PCI inflammatory status continue to be significant predictors of patient outcomes in the modern era of DES. Complex interactions between cellular and humoral inflammation, as well as the extent of PCI-induced vascular injury, hinder the identification of effective anti-inflammatory treatments. Identification of specific key targets of inflammation is necessary to allow for a more targeted immunomodulatory approach to improve patient outcomes.

Key messages

- Pre- and post-PCI inflammatory status remain significant predictors of patient outcomes in the drug eluding stent era
- The complicated inflammatory cascade has hindered the identification of effective anti-inflammatory treatments
- A more targeted immunomodulatory approach is necessary to improve patient outcomes

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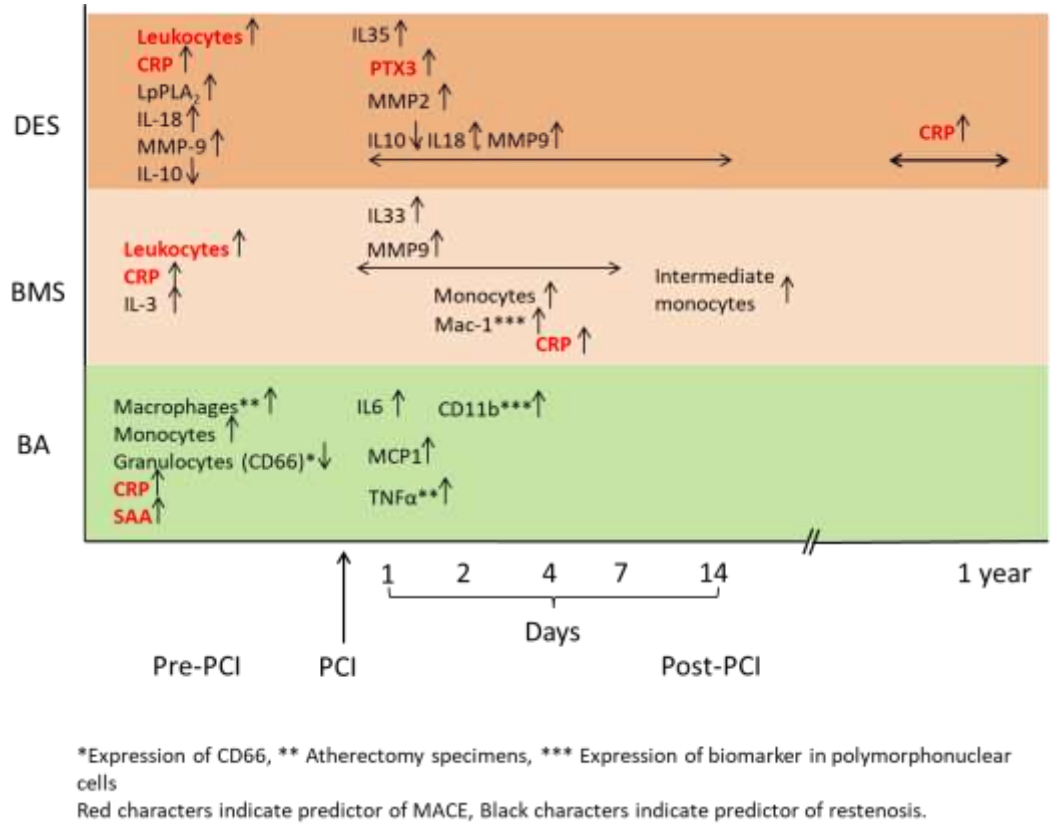

Fig 1: Timeline of inflammation in angioplasty. Schematic representation of pre- and post-PCI inflammatory biomarkers predicting patient outcomes following angioplasty

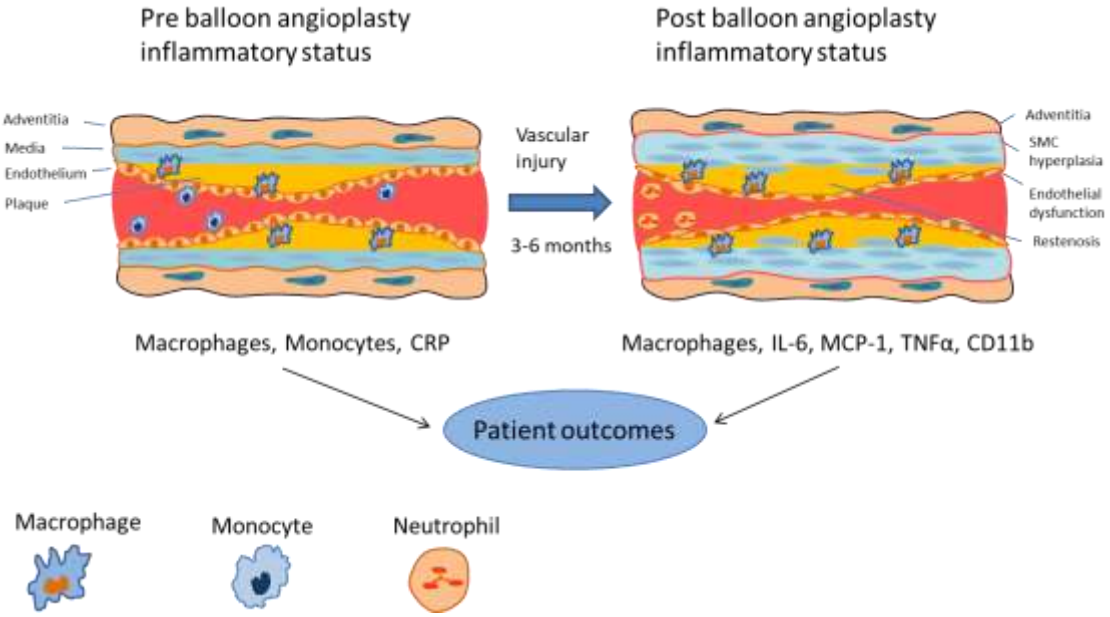

Fig 2: Role of inflammation in balloon angioplasty. Schematic representation of how the inflammatory biomarkers pre- and post- balloon angioplasty can predict patient outcomes.

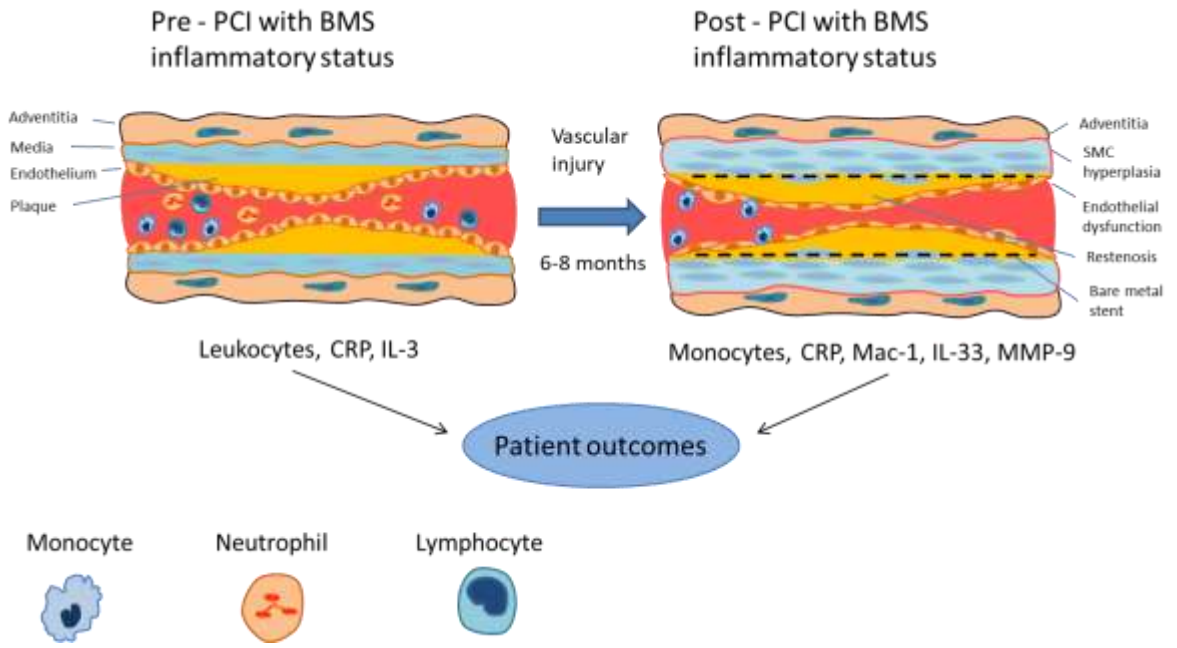

Fig 3: Role of inflammation in angioplasty with bare metal stent. Schematic representation of the biomarkers shown to be predictors of patient outcomes in angioplasty with bare metal stent

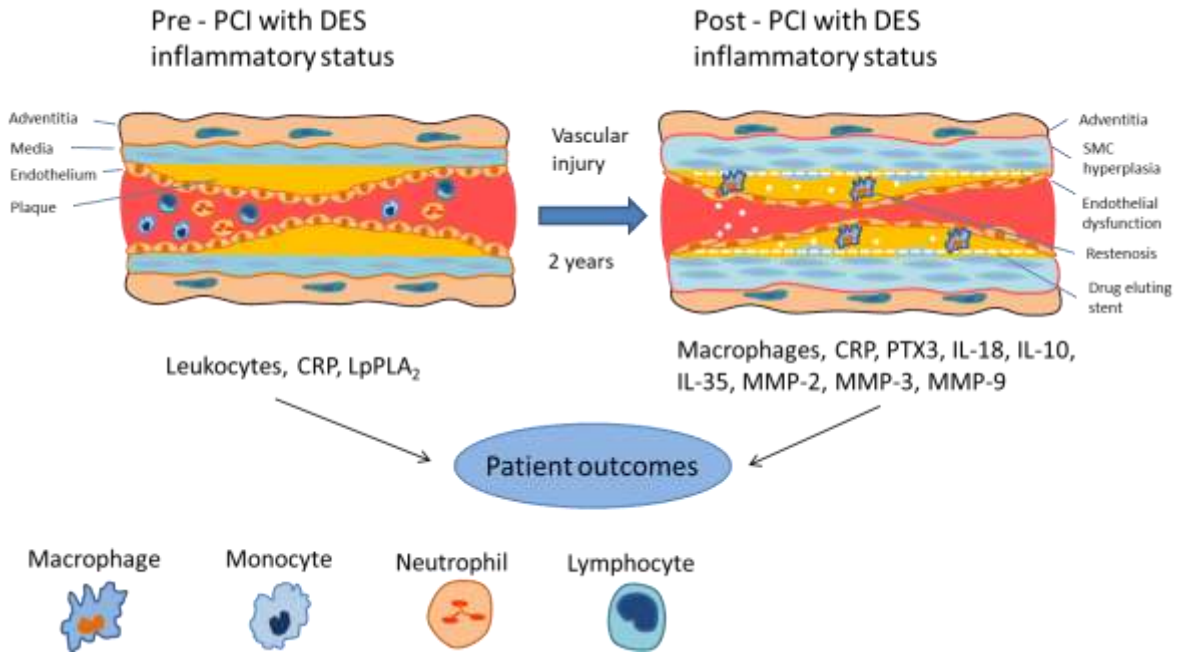

Fig 4: Role of inflammation in angioplasty with drug eluting stent. Schematic representation of biomarkers shown to be predictors of patient outcomes in angioplasty with drug eluting stent

<table>
<tr><th colspan="4">Percutaneous coronary intervention</th></tr>
<tr><td>Direct endothelial injury</td><td>Reperfusion induced ROS</td><td colspan="2">Release of necrotic core contents</td></tr>
<tr><td colspan="2">Cytokine response</td><td>Neutrophil extracellular traps (NETs)</td><td>Microemboli</td></tr>
<tr><td colspan="2">Leukocyte and platelet activation</td><td>NLRP3 inflammasome leading to IL1β and IL6 response</td><td>Inflammatory response due to distal obstruction</td></tr>
</table>

Table 1: Key mechanisms of PCI-induced inflammatory response. Table summarising the main mechanisms involved in PCI induced inflammatory response.

Abbreviations: ROS; reactive oxygen species, NETs; neutrophil extracellular traps, NLRP3; NOD-like receptor protein 3

Treatment	**Effect on PCI-induced inflammation**	**Effect on clinical endpoints**
Statins	Reduction	Improvement
Colchicine	Possible	No effect

Table 2: Key treatment strategies for PCI-induced inflammation. Table summarising the main treatment strategies to reduce PCI-induced inflammation