Coronary Stenting and Inflammation: Implications for Further Surgical and Medical Treatment

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The introduction of percutaneous coronary interventions (PCI) with stent implant has substantially shifted the treatment of coronary artery disease. The current approach to coronary artery disease treatment includes first-choice PCI in selected subgroups; and once this therapy fails, frequently the patient is referred for coronary artery bypass graft surgery. However, evidence of chronic inflammatory reaction and endothelial dysfunction after PCI has been emerging and that might be interfering with patient outcome when surgical or medical treatments are subsequently required. The clinical significance of these complications after PCI, herein examined, has been less studied and needs better assessment. Also, the premise that coronary artery bypass graft surgery can safely be performed in patients with coronary stenting failure may not hold true, as graft patency might be adversely affected. Furthermore, the superimposed inflammatory reaction may blunt the efficacy of medical treatment.

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REVIEWS

The introduction of percutaneous coronary interventions (PCI) with stent implant has substantially shifted the treatment of coronary artery disease. The current approach to coronary artery disease treatment includes first-choice PCI in selected subgroups; and if this therapy fails, the patient is often referred for coronary artery bypass graft (CABG) surgery. However, novel complications associated with inflammatory reaction after PCI have been emerging and might be interfering with patient outcome when surgical or medical treatments are subsequently required.

Stents have evolved from the early concept of providing support to prevent vessel recoil and negative remodeling, becoming elaborate devices, and have culminated with the highly sophisticated technology of drug-eluting stents.

However, unlike balloon angioplasty, in which elastic recoil and vessel remodeling play an important role for vessel luminal loss in the long term, restenosis after coronary stenting takes place because of neointimal proliferation. It also bears a relationship to the extent of the vessel injury and inflammatory response [1].

Recent evidence has demonstrated that implant of coronary stents evokes the advent of a local and systemic inflammatory response syndrome [2–8], and restenosis comprises only part of the manifestation of the inflammatory reaction. The consequent endothelial dysfunction and ischemia are connected events that have not been well studied.

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Pathophysiology of Vascular Injury and Restenosis

Experimental animal and human autopsy studies have demonstrated that local arterial reaction to balloon dilatation and stenting follow a response-to-injury sequence of events. In human studies, coronary stents are shown to elicit an initial acute inflammatory cell response within 0 to 3 days, centered at the stent struts, the severity of which is related to the trauma to the vessel wall. Stimulus for the inflammatory and restenosis process is disruption of the coronary endothelial layer. That promptly activates inflammatory cells, with early neutrophil recruitment to the injury site, followed by prolonged macrophage accumulation [9].

By 2 to 4 weeks, acute inflammation subsides and is replaced by chronic inflammatory cells, along with proliferating smooth muscle cells associated with organizing thrombus and a thin provisional extracellular matrix. Beyond 30 days, fibrin and chronic inflammation persist, and smooth muscle cells and extracellular matrix (proteoglycans and collagen) further enrich the expanding neointima [10].

Coronary stenting appears to cause a deeper arterial injury and a more intense inflammatory response into the vessel wall than does balloon angioplasty [11]. Balloon angioplasty is followed only by an early neutrophil infiltration and, in contrast, in stented arteries early neutrophil recruitment is followed by prolonged and abundant recruitment of macrophages within the neointima [11, 12].

The inflammatory reaction triggered by the stent insertion is maintained by several concomitant factors. Besides the mechanism of stent expansion with vessel wall rupture, there are the superimposed permanent radial mechanical strain applied to arterial wall, the

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presence of an intravascular residual metallic foreign material, and ischemic phenomena induced by endothelial dysfunction. The stent struts cause focal deep vascular trauma, and it has been demonstrated that the initial inflammatory reaction is more accentuated at the points of greatest strain of the stent struts on the arterial wall [12].

Additionally, the main inflammatory and proliferative reactions are not limited to the vessel wall but rather extend from the injured vessel throughout the surrounding tissues, including adjacent myocardium [5, 13].

Inflammatory Markers After Stenting

To date, several studies have demonstrated that PCI induces the release of multiple inflammatory markers [8, 14, 15] that are associated with a later poor prognosis [16].

Clinical investigations have shown that PCI with stent implant results in leukocyte and platelet activation, both locally in the coronary sinus and systemically in the peripheral circulation. It also increases the expression of adhesion molecules, and formation of platelet–leucocyte complexes [17]. Patients expressing high levels of cellular activation are at higher risk for restenosis and cardiac events after successful PCI with stent implant [18].

Rajagopal and associates [16] found that after PCI, white blood cell counts were an independent predictor of long-term mortality and a significant predictor of mortality in the subgroup of patients with an increase in postprocedural creatine kinase–myocardial band (CK-MB) values. Fukuda and associates [19] found that circulating monocytes raise after coronary stent implantation, and the peak monocyte count was related to in-stent neointimal volume. In coronary sinus, blood samples taken 15 minutes after angioplasty showed an augmented expression of adhesion molecules on the surface of neutrophils and monocytes [20], whereas interleukin-6 (IL-6) levels increased as early as after 1 hour [21].

Adverse late clinical outcomes are linked to the magnitude of the systemic inflammation and patients undergoing PCI may be risk stratified according to an increase in concentrations of inflammatory markers before percutaneous intervention as well as an increase in their concentrations afterward [22].

Navarro-Lopez and colleagues [23] demonstrated that at 6 months of follow-up, patients with stent restenosis presented amplified inflammatory activity expressed by a rise of the cytotoxic T lymphocytes CD3+/CD56+ and activated monocytes CD11b. Plasma concentrations of IL-6 and tumor necrosis factor alpha (TNF-α) increased significantly after the intervention, but only TNF-α concentrations remained high at 6 months [23].

Current studies demonstrated that stent deployment is associated with an increase in C-reactive protein (CRP), and this rise on CRP level was significantly higher in stable plaques rather than unstable plaques. Elevated circulating values of CRP, a sensitive systemic marker of inflammation, shows a significantly increased risk of plaque rupture and coronary events [2, 4, 6–8, 24]. In fact, the most notable association of outcomes and CRP has been with mortality and, to a lesser extent, with myocardial infarction [24].

Almagor and colleagues [2] showed that CRP levels in patients after coronary stent implantation were persistently high and a correlation between increases in the CRP concentration after PCI with stenting and adverse events was also reinforced. Elevation of CRP has been shown to predict death during follow-up after PCI [7, 9]. Additionally, after PCI with stenting, it has been suggested that an increased serum level of CRP is associated with progression of disease at areas remote from the initial stented lesion, and not necessarily to in-stent restenosis per se [25].

An increase in lipid peroxidation accompanied by a reduction in the stable end products of nitric oxide in plasma was observed in patients with stent restenosis several months after PCI. Oxidative stress appears to be involved in several processes that contribute to atherogenesis [26]. Additionally, data from experimental and human studies have suggested that oxidized low-density lipoproteins contain vasoactive moieties, and it is possible that release of such vasoactive substances during PCI may lead to vasoconstriction of the microvasculature and no-reflow phenomenon [27]. Cutlip and associates [28] found that the clinical outcome beyond 1 year after stenting is determined by a high rate of events related to disease progression in coronary segments other than the stented lesion, which itself remains relatively stable [28].

Significant clinical and angiographic stent restenosis occurs in roughly one third of patients with bare stents, but varied grades of restenosis take place in all stented arteries [29].

Several diseases are presently known to evolve with a pattern of persistently high inflammatory markers; the pathogenesis of these diseases, such as cardiovascular and degenerative diseases, infections, and cancer, have been linked to chronic inflammatory processes [30]. Recent studies have identified the role of proinflammatory mediators and endothelial dysfunction in the development and progression of heart failure [31].

Post-Stenting Endothelial Function

Chronic inflammation induces cytokine hypersecretion and eventually leads to changes in endothelial mediators releasing. An enhanced circulating level of proinflammatory cytokines resulting in persistent low-grade inflammation are associated with endothelial dysfunction and is deleterious for vascular functions.

Endothelial damage is a major cause of postangioplasty restenosis [9]. The harm to endothelial function during angioplasty decreases the availability of vasculoprotective molecules such as nitric oxide (NO) and prostacyclin as well as antioxidant systems, with a concomitant increment in the production of growth-promoting substances [32].

Patients who underwent PCI exhibited more severe endothelial dysfunction in the long term after stenting when compared with balloon angioplasty or direct rota-