Selectin Blockade Reduces Neutrophil Interaction With Platelets at the Site of Deep Arterial Injury by Angioplasty in Pigs

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Abstract—The adhesion of neutrophils to damaged arterial surfaces is increased in the presence of platelets by a mechanism implicating platelet P-selectin. Such interactions may enhance thrombus formation and the vascular response to injury. In this study, we investigated the effects of a selectin blocker (CY-1503), an analogue of sialyl Lewisx, on platelet and neutrophil interactions after arterial injury produced by angioplasty in pigs. 51Cr-platelet deposition and 111In-neutrophil adhesion were quantified on intact, mildly and deeply injured carotid arterial segments, produced by balloon dilation, in control (saline, n = 8) and treated (CY-1503, 15 mg/kg IV, n = 7) pigs. The hematological parameters, the aggregation of whole blood in response to adenosine diphosphate, and the activating clotting time, as well as the heart rate and mean arterial blood pressure, were similar among groups and were not influenced significantly by CY-1503. The level of platelet and neutrophil adhesion increased significantly with the severity of arterial injury but was not influenced by CY-1503 on intact and mildly injured arterial segments. However, at the site of deep arterial injury, CY-1503 treatment was associated with a 58% reduction (P < 0.01) in neutrophil adhesion, from 446.7 ± 72.6 × 103 neutrophils/cm² in the control group to 186.8 ± 38.7 × 103 neutrophils/cm² in the CY-1503–treated group, whereas platelet deposition remained unchanged (43.4 ± 15.6 × 10⁶ platelets/cm² versus 50.1 ± 12.2 × 10⁶ platelets/cm² in the control group). In in vitro adhesion experiments, using isolated platelet and neutrophil suspensions, we found that CY-1503 interfered with the adhesion of neutrophils to damaged arterial surfaces only in the presence of platelets. In contact with thrombogenic arterial surfaces, adherent and activated platelets supports neutrophil adhesion at the site of deep injury by an adhesive interaction involving neutrophil sialyl Lewisx. The inhibitory effect of CY-1503 on neutrophil interaction with adherent platelets may be clinically relevant in patients undergoing percutaneous transluminal coronary angioplasty where platelet and neutrophil interactions may enhance the acute and chronic arterial response to injury. (Arterioscler Thromb Vasc Biol. 1999;19:372-377.)

Key Words: platelets ■ neutrophils ■ angioplasty ■ selectin ■ CY-1503

The interactions of platelets and leukocytes with the endothelium and the subendothelial matrix are essential to maintain vascular homeostasis. Dysregulation of these interactions after arterial injury has been implicated in thrombogenesis, atherosclerosis, vasospasm, restenosis, and a variety of inflammatory processes.1–3 The extent of platelet and neutrophil accumulation is influenced by the severity of arterial injury and regulated by the relative interplay of adhesion molecules, procoagulant proteins, the local shear conditions, and the nature of the arterial surface exposed. Under pathophysiological conditions, neutrophil-derived products such as platelet activating factor, proteolytic enzymes, reactive oxygen metabolites, and leukotrienes can amplify vascular injury and platelet activation.4–6 Conversely, platelet stimulation can enhance neutrophil activation and adhesion.7–9 The complexity of these interactions between platelets and neutrophils is well recognized. However, the nature and mechanisms of these interactions after arterial injury are being explored.

In previous studies, we have shown a close interaction between platelets and neutrophils at the sites of carotid arterial injury produced by balloon dilation in pigs.10 In this model, we have found that platelet depletion was associated with decreased neutrophil adhesion to damaged arterial surfaces,11 confirming our previous findings showing increased neutrophil adhesion in the presence of platelets12 in a concentration-dependent manner.11 These studies provide strong evidence for platelet involvement in neutrophil adhesion to damaged arterial surfaces. The interaction between platelets and neutrophils have been shown to be dependent on P-selectin (CD62P, GMP-140, or PADGEM) expression on activated platelets.13 The selectins are named according to the
cell type on which they were originally identified: P-selectin (platelets), E-selectin (endothelium), and L-selectin (lymphocytes). P-selectin is present in the α-granules of platelets and in the Weibel-Palade bodies of endothelial cells and is implicated in many homotypic and heterotypic reactions including the interactions of neutrophil with endothelial P- and E-selectin. Neutrophil-neutrophil L-selectin, and neutrophil with platelet P-selectin. These pathways highlight the importance of selectins in neutrophil adhesion. Therefore, blockade of selectins or their ligands could reduce neutrophil accumulation in many inflammatory reactions and thrombotic events.

The selectin family is characterized by adhesive interactions that involve fucosylated oligosaccharides on opposite cells, such as sialyl Lewisx (sLeX). Analogues of this carbohydrate-binding site, a sLeX oligosaccharide containing fucose and sialic acid moieties [NeuAC2,3Galβ1,4(Fucol,3)GlcNAcβ1,3Galβ-O(CH2)5COOCH3] such as CY-1503, inhibit neutrophil adhesion to endothelial selectins in vitro and in experimental models of myocardial ischemia and reperfusion in vivo. Recently, it has been shown that a carbohydrate analogue of sLeX reduced cyclic flow variations in injured canine coronary arteries and attenuated intimal hyperplasia after balloon arterial injury in rabbits. However, none of those studies have examined platelet and neutrophil adhesion and interactions with the damaged denuded arteries, which may be the first target of sLeX analogues during the acute response to arterial injury. Accordingly, this study was designed to study platelet and neutrophil interactions with different degrees of arterial injury, such as that occurring after balloon dilation, and the effects of a selectin blocker (CY-1503) on these interactions.

Methods

Animal Preparation

Fifteen 6- to 8-week-old, normal cross-breed Yorkshire pigs of either sex weighing 18.5 ± 0.6 kg were prepared in accordance with the guidelines of the Canadian Council on Animal Care regulations, as previously described. The animals were sedated by intramuscular injection of 20 mg/kg ketamine and 3 mg/kg azaperone, intubated, and mechanically ventilated with O2/air. Anesthesia was maintained with 0.5% to 1% halothane. The hematologic parameters of each animal were determined, and the electrocardiogram and blood pressure were monitored.

Isolation and Labeling of Platelets and Neutrophils

Fifty mL of autologous blood anticoagulated with acid-citrate dextrose was collected from the cranial vena cava and used to obtain a platelet-rich plasma by differential centrifugation, as previously described. After washing, each platelet suspension was incubated with 300 µCi 51Cr (Amersham International) for 40 minutes. The suspension was centrifuged to remove unbound 51Cr, and the radiolabeled platelets were then resuspended in 5 mL of platelet poor plasma and reinjected into the animal. Neutrophil isolation was performed using the pellet obtained after the first centrifugation of the blood used in platelet preparation according to a method previously reported. This method involves sedimentation with 4% dextran, centrifugation on Ficoll-Paque gradient and hypotonic lysis of red blood cells. The isolated neutrophil suspension was incubated with 250 µCi of 111In-tropolone (Merck Frosst Canada Inc) for 30 minutes. The suspension was centrifuged to remove unbound 111In, and the radiolabeled neutrophils were then resuspended in 5 mL of platelet poor plasma and reinjected into the animal. This procedure yielded a neutrophil preparation that is over 95% pure and viable, as assessed by the trypan blue exclusion test.

Experimental Groups and Carotid Arterial Injury

Carotid injury was performed using a 7F-polyethylene balloon dilation catheter (size, 8 mm × 3 cm, Meditech Inc), as previously described. A 9F-introducer sheath was inserted into the right femoral artery for introduction of the balloon dilation catheter, and an 8F-introducer sheath was inserted into the femoral vein for blood sampling and drug infusion. Five minutes before the angioplasty procedure, animals received either CY-1503 (15 mg/kg, IV bolus, n = 7) (Cytel Corporation) or saline (IV, n = 8). CY-1503 has a large volume of distribution and is rapidly excreted through the kidney with half life less than 20 minutes in cats and rats. Given that our procedure lasts only 30 minutes this dose of 15 mg/kg bolus was chosen, based on computer allometric pharmacokinetic modeling provided by Cytel, to maintain a plasma concentration of more than 20 µg/mL during the study and sufficient to block selectins. After a single bolus of heparin (100 IU/kg IV), the balloon dilation catheter was inserted into the right femoral artery and advanced under fluoroscopic control into the left and right common carotid arterial segments between the fifth and fourth cervical vertebrae. Five inflations were performed at a single interval, each for 30 seconds with a 60-second interval between each inflation. In all pigs, angiograms of the common carotid arteries were obtained before and during angioplasty and were used to determine the exposed diameter and the balloon-to-artery ratio for each artery.

The dilation procedure was successful in 14 arteries in the control and in 13 arteries in the treated groups. Two left carotid arteries in the control and 1 right carotid artery in the treated group were excluded from the study because balloon dilation induced a more deep injury extending to the adventia with rupture of these arteries and formation of an occlusive thrombus.

Quantification of Platelet and Neutrophil Deposition

At the end of the experiments, approximately 30 minutes after angioplasty, the carotid arteries were perfusion-fixed in situ with a buffered solution of 2% glutaraldehyde and 1% parafomaldehyde, as previously described. The fixed carotid arteries were then removed and cleaned of all adventitial tissue. The dilated portion was divided into 3 segments, and the internal diameter and length of each segment were measured to determine the surface area (cm²). Nondilated segments with intact endothelium were also selected and measured. After surface measurements, the radioactivity of each segment as well as that of reference blood samples was counted in a gamma counter (Minaxi 5000, Packard Instruments Co) equipped with a computer and a multichannel analysis program. Knowing blood platelet and neutrophil counts and the radioactivity of 51Cr and 111In in blood and on the arterial segments, platelet (×10⁶) and neutrophil (×10⁶) deposition per cm² was calculated as previously reported.

Histological Analysis

After radioactivity counting, representative 2 to 3 mm sections from each arterial segment were processed and embedded in paraffin. Cross-sections (4 µm) were stained with Movat pentachrome stain, which produces intense staining of the internal and external elastic lamina. All specimens were evaluated microscopically for the presence of mild or deep arterial wall injury, which is characterized by the presence of tears through the internal elastic lamina with the exposure of the arterial media. Morphometric analysis was performed on each section of the deeply injured segments to quantify the extent of injury. The number of internal elastic laminar tears and the arc length of the internal elastic laminar fracture (fracture length), traced from 1 dissected laminal end to the other, were used as a measure of the extent of injury. The circumference demarcated by the internal elastic lamina was also measured, and the ratio of fracture length-to-internal elastic lamina was calculated to correct for vessel size.
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The flow within the portion of the subjacent media, and cut to fit within the superfusion chamber was adjusted at 10 mL/min with a peristaltic pump. The flow was performed within the first minute after blood sampling. The amplitude of aggregation was measured in ohms 5 minutes after the addition of the agonist.

Aggregation Study

Aggregation was performed using a whole-blood aggregometer (Chronolog Corp) and fresh blood samples obtained before and after the administration of CY-1503. Aggregation was induced by adding 50 μL of the platelet agonist adenosine diphosphate (10 μmol/L) to 450 μL of anticoagulated blood (5 U/mL heparin). All measurements were performed within the first minute after blood sampling. The amplitude of aggregation was measured in ohms 5 minutes after the addition of the agonist.

Isolated Platelet and Neutrophil Adhesion Assay

To determine the influence of the selectin blocker on isolated neutrophils adhesivity to platelets, we have performed an in vitro adhesion assay. In these experiments, we have used Plexiglas superfusion flow chambers that mimic the tube-like and cylindrical shape of blood vessels. 1,2,37,38 Each chamber contains a window (2.0 mm ID) allowing direct exposure of damaged arterial segments to isolated neutrophils suspensions mixed or not with platelets. These damaged arterial segments were prepared from porcine aortas, which were dissected free of surrounding tissues, cut into rings, and longitudinally opened. Damaged arterial segments were then prepared by lifting and peeling off the intima, together with a thin longitudinally opened. Damaged arterial segments were then pretreated for 5 minutes with saline or 200 μg/mL of CY-1503 before adding or not platelets (250×10^6/mL). The arterial tissues were then removed and the radioactivity counted in a gamma counter. The level of neutrophil adhesion, expressed as neutrophils×10^6/cm², was then calculated.

Statistical Analysis

Results are expressed as mean±SE. Intergroup analyses were performed using Student’s unpaired t test and intragroup comparisons were assessed by Student’s paired t test and when appropriate by 1-way ANOVA. Differences were considered statistically significant at the 95% confidence level (P<0.05).

Results

Group Characteristics

The characteristics of the isolation and labeling procedures of platelets and neutrophils were similar in both groups as shown in Table 1. Table 2 shows platelet and leukocyte counts in the circulation, platelet aggregation in response to 10 μmol/L adenosine diphosphate, the activating clotting time, heart rate, and mean arterial blood pressure at baseline and after injection of saline or CY-1503 in the control and treated groups, respectively. Compared with baseline, only platelet count decreased significantly in both the control and CY-1503 groups by 22% and 20%, respectively. The reason for this decrease in platelet count is unknown but may be related to animal preparation and anesthesia. However, our results cannot be influenced by this change because this decrease was similar in both groups, and the platelet counts were statistically similar before the angioplasty procedure in the control (349.8±38.1×10^9/mL) and in the CY-1503 (477.1±66.7×10^9/mL) groups. All the remaining parameters were within the normal range at baseline and were not changed significantly after the injection of the selectin blocker CY-1503.

Angiographic and Histological Analyses

Table 3 summarizes the characteristics of the dilated arteries in the control and CY-1503–treated groups. The diameter of these arteries and the balloon/artery ratio averaged 4 mm and 1.1 to 1.2, respectively, and were statistically similar in both groups. In the deeply damaged segments, the fracture length of the internal elastic lamina as determined by the histological and morphometric analyses was also similar between the control and CY-1503–treated groups, indicating that the extent of injury was comparable in both groups.

Platelet and Neutrophil Adhesion In Vivo

As illustrated in Figure 1, platelet deposition on the dilated segments with deep injury was significantly much higher than those quantified on mildly injured segments with endothelial denudation or on uninjured segments with intact endothelium.

| Table 2. Hematologic and Hemodynamic Parameters in the Control and CY-1503 Treated Groups |
|----------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                      | Control         | Placebo         | Treated         | CY-1503         |
| Platelets, ×10⁹/mL                    | 449.0±27.2      | 349.8±38.1*     | 600.1±75.8      | 477.1±66.7*     |
| Leukocytes, ×10⁶/mL                   | 23.2±2.1        | 21.5±2.1        | 19.8±2.6        | 18.1±3.0        |
| Platelet aggregation, ohms            | 14.9±3.8        | 15.3±3.5        | 13.0±2.9        | 9.6±1.7         |
| ACT, s                                 | 115.0±6.2       | 118.5±5.5       | 126.8±5.6       | 125.8±5.9       |
| Heart rate, bpm                        | 108.7±5.1       | 116.5±8.1       | 116.6±9.8       | 114.9±10.2      |
| Mean arterial BP, mm Hg               | 60.7±3.1        | 62.4±3.3        | 61.2±3.3        | 60.0±4.8        |

ACT indicates activating clotting time; BP, blood pressure.
*P<0.05 versus baseline.
in both groups. There was no statistical difference in platelet deposition on deeply injured segments between the control (50.1±12.2×10⁶ platelets/cm²) and the CY-1503 (43.4±15.6×10⁶ platelets/cm²)–treated groups.

In the control group, neutrophil adhesion (Figure 2) increased significantly with the severity of arterial injury from 26.1±7.9×10³ neutrophils/cm² on intact endothelium to 252.6±49.1×10³ neutrophils/cm² on denuded segments with mild injury and to 446.7±72.6×10³ neutrophils/cm² (P<0.05) on deeply injured segments. CY-1503 treatment was associated with a significant (58%, P<0.01) decrease in neutrophil adhesion (186.8±38.7×10³ neutrophils/cm²) on deeply injured segments, whereas neutrophil adhesion to segments with intact endothelium or mildly injured was not influenced by CY-1503 treatment.

**Neutrophil Adhesion In Vitro**

To assess whether CY-1503 interfered directly with the adhesive function of neutrophils or with platelet-neutrophil adhesive interactions, we have performed in vitro adhesion experiments in which isolated neutrophils or mixed neutrophil and platelet suspensions were pretreated with CY-1503 or saline and then exposed to damaged arterial surfaces under flowing conditions. The results are presented in Figure 3 and show that CY-1503 did not interfere with the adhesive function of isolated neutrophils but significantly inhibited (P<0.01) the increased adhesion of neutrophils in the presence of platelets.

**Discussion**

Following balloon angioplasty, rupture of the internal elastic lamina with exposure of the arterial media is characterized by extensive platelet and neutrophil adhesion, which collaborates to enhance the arterial response to injury. Administration of the analogue of sLex or the selectin blocker CY-1503 led to a significant reduction in neutrophil adhesion to the highly thrombogenic arterial surfaces without any significant effect on platelet deposition or on the adhesion of isolated neutrophils in the absence of platelets. These results indicate that at the site of deep arterial injury adherent and activated platelets contribute to neutrophil recruitment via sLex.

The receptors implicated in the adhesion and aggregation of platelets, as well as the pathological significance of these interactions with the vessel wall, have been relatively well characterized. Cell adhesion molecules involved in platelet adhesion and aggregation, such as glycoprotein (GP)Ia/Ib (αIβI integrin) and GPIIb/IIIa (αIIbβI integrin), enhance thrombus formation in association with the coagulation pathway and leukocyte integrins. Also, platelets possess P-selectin involved in platelet-leukocyte-endothelial interactions, platelet/endothelial cell adhesion molecule (CD31) involved in platelet-platelet binding, and GPIV (CD36) involved in platelet adhesion to collagen. The adhesion of platelets to damaged arterial surfaces is regulated by the interactions between these GPs, the von Willebrand factor, fibronectin, collagen, and other procoagulant proteins found in plasma and on the exposed arterial surface. As demonstrated previously, the current study confirms that platelet deposition is influenced by the nature of the arterial surface exposed and increases with the severity of arterial injury. In fact, compared with deep injury, mildly injured arterial surface is less thrombogenic and causes mild platelet deposition (<10⁶/µl).
cm²). This type of mild injury is characterized by endothelial denudation and intimal damage with intact elastic lamina. Indeed, the initial binding of platelets to this surface does not require activation and is predominantly mediated by the interaction of platelet GPIb/IX with the von Willebrand factor and the GPIIb/IIIa on nonactivated platelets with immobilized fibrinogen. In contrast, deep arterial injury, which is characterized by rupture of the internal elastic lamina and exposure of the tunica media, is more thrombogenic than the subendothelium. The exposure of the arterial media to flowing blood uncovers collagen, fibronectin, laminin, and thrombospondin in an uneven boundary layer that leads to extensive platelet adhesion and aggregation through GPIIb/IIIa and contributes significantly to thrombus growth. Under normal conditions, the intact endothelium sequesters the adhesive GP ligands from the platelet in the subendothelium, thus preventing platelet adhesion in the absence of vascular damage. Given that platelet adhesion and aggregation are mediated primarily by the integrin family of adhesion molecules, it is not surprising that the selectin blocker (CY-1503) does not influence platelet deposition on any type of the arterial surfaces exposed after angioplasty nor platelet aggregation in whole blood. In contrast, Ueyama et al have found that a high dose (40 mg/kg), but not a low dose (5 mg/kg), of an analogue of sLeα reduced cyclic flow variations, which are mainly mediated by platelet adhesion and aggregation, in a canine model of stenosed and endothelium-injured coronary arteries. Although our experimental porcine model of balloon carotid injury is different from that of stenosed and endothelium-injured coronary arteries model, our results indicate that CY-1503, at 15 mg/kg, selectively reduced neutrophil adhesion to deeply damaged arteries without any significant effect on platelets.

In previous studies aimed to determine the influence of platelets on neutrophil adhesion, we have shown a close interaction between platelets and neutrophils after arterial injury in vitro and in vivo. We have found that thrombocytopenia or platelet depletion was associated with decreased neutrophil adhesion to damaged arterial surfaces by angioplasty, indicating that platelets support neutrophil adhesion. This reaction involves cell-cell interactions that are at least mediated by platelet P-selectin. In another study involving an in vivo thrombosis model, platelets have been shown to adhere to vascular grafts, express P-selectin, and, subsequently, to bind leukocytes through P-selectin. This was also demonstrated in in vitro vessel wall injury models.

In the current study, we have used a more clinically relevant animal model to produce different degrees of arterial injury such as that occurring after atherosclerotic plaque rupture or after balloon angioplasty. We have observed that, similar to platelet deposition, neutrophil adhesion is also influenced by the extent or severity of arterial injury. Interestingly, the selectin blocker (CY-1503) significantly inhibited neutrophil adhesion only on the deeply injured arterial segments, without any significant effect on platelet deposition. This finding suggests that, in the presence of deep arterial injury, platelet adhesion and activation may lead to P-selectin expression that, in turn, can fix neutrophils via an interaction with sLeα and contribute to increase neutrophil adhesion as an acute reaction to the thrombogenic stimulus produced by angioplasty. Our finding that CY-1503 did not interfere directly with neutrophils, as the adhesion of isolated neutrophil suspensions to damaged denuded arterial segments in vitro was not influenced by CY-1503 but was inhibited in the presence of platelets, indicates that the selectin blocker acts on the adhesive interactions between neutrophils and platelets and that neutrophil-neutrophil homotypic adhesion via L-selectin and PSGL-1 is less important in these interactions. Balloon angioplasty induces a complete denudation of the arteries at the site of dilation, thus excluding any possible effects of CY-1503 on neutrophil adhesion to endothelial P- or E-selectin. In addition, neutrophil adhesion to normal adjacent arterial segments with intact endothelium was similar between the control and CY-1503 groups. Neutrophil-endothelial cell adhesion is controlled by different steps involving L-selectin on resting neutrophil, β₂-integrin on activated neutrophils and ICAM-1, and P- and E-selectin on activated endothelial cells. Our study was performed without prior activation of neutrophils or the endothelium. Under these conditions, neutrophil interaction with endothelium was minimal and was not influenced by the selectin blocker. In the absence of endothelium, it has been shown that neutrophils can roll on immobilized platelets or adhere via platelet P-selectin or neutrophil β₂-integrin. Many studies have reported that other mechanisms may be implicated in platelet binding to neutrophils, such as (1) fibrinogen bridging via platelet GPIIb/IIIa and neutrophil MAC-1, (2) thrombospondin bridging via GPla/Ia, GPIIb/IIIa, or GPIV on platelets and a specific receptor on neutrophils, (3) platelet ICAM-1 binding to neutrophil LFA-1, and (4) immune complex interactions between platelet Fc RII (CD32) and neutrophil Fc RIIb (CD16). These different mechanisms for neutrophil interactions with platelet and recruitment to damaged arterial surfaces may explain the lack of complete inhibition, by CY-1503, of neutrophil adhesion in our study.

The importance of neutrophil-platelet adhesive interactions has been noted in the circulation of patients with unstable angina and after coronary angioplasty. Recently, it has been shown that blockade of the selectins with an analogue of sLeα reduced intimal hyperplasia after balloon injury in rabbits. Our study highlights these interactions at the site of arterial injury produced by angioplasty through an adhesive interaction between platelets and neutrophil sLeα. The inhibitory effect of the selectin blocker may be clinically relevant because neutrophil-platelet interactions after angioplasty appears to play an important role in the initial step of the arterial response to injury and may accelerate the pathophysiologic chain reaction of restenosis.

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