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Review

Pathophysiology and therapeutic modification of thrombin generation in patients with coronary artery disease

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Abstract

Thrombin plays a central role in thrombogenesis: it activates platelets, converts fibrinogen to fibrin, and activates factor XIII, which then crosslinks and stabilizes the fibrin clot. In addition, thrombin amplifies coagulation by activating factors VIII and V, key cofactors in the generation of activated factor X and thrombin, respectively. Even platelet function is influenced by thrombin. Hence, thrombin generation is most important both in the chronic progression of coronary atherosclerotic disease and in its conversion to acute events. To date, various therapeutic approaches capitalize on this knowledge by targeting specific thrombin-related pathways. Among the succesful and carefully documented pharmacologic strategies in acute or chronic coronary heart disease are the use of unfractioned heparin, low-molecular-weight heparin, thrombolysis, hirudin, and/or inhibition of thrombin generation by glycoprotein IIb/IIIa antagonists, most often utilized on top of antiplatelet theraphy (e.g., with acetylsalicylic acid) and/or vitamin K antagonism. The present review provides insights into the pathophysiology of thrombin generation in coronary atherosclerosis and gives an overview over the above mentioned therapeutic thrombin modifications.

Keywords: Thrombin; Coronary artery disease; Coagulation; (Human)

1. Pathophysiology of acute coronary syndromes

Coronary artery thrombosis superimposed on a disrupted atherosclerotic plaque has emerged as the pivotal pathophysiologic event in acute coronary syndromes (i.e., unstable angina, myocardial infarction and sudden death; Davies and Thomas, 1985; Falk, 1985; Fuster et al., 1992). The thrombotic response to plaque rupture involves both platelet activation and thrombin generation (Fig. 1; Vanhoutte, 1997). The arterial wall injury, associated with plaque disruption, exposes highly thrombogenic components of subendothelial structures, such as von Willebrand factor and collagen to flowing blood (Fuster and Lewis, 1994). The thrombogenicity of the plaque is influenced by tissue factors and thromboxane, synthesized by lipid-laden foamy macrophages and predominantly localized in the necrotic core of the plaque (Fitzsimmons et al., 1999; Wilcox et al., 1989). Exposed tissue factor binds factor VII/VIIa and this complex then triggers thrombin generation by activating factors IX and X (Fig. 2; Nemerson, 1988). In addition to activation of the coagulation cascade through tissue factor expression, plaque disruption with thrombus formation is associated with activation of the factor XII–kallikrein–kinin system, as well as with fibrinolysis (Hoffmeister et al., 1985).

2. The role of thrombin in thrombogenesis

Thrombin plays a central role in thrombogenesis (Fig. 1). It activates platelets, converts fibrinogen to fibrin, and activates factor XIII, which then crosslinks and stabilizes the fibrin clot. In addition, thrombin amplifies coagulation by activating factors VIII and V, key cofactors in the generation of activated factor X and thrombin, respectively (Fig. 1). The sensitivity of the platelets to activation by thrombin leads to further thrombus growth, and thrombin becomes internalized in the lesion as the plaque grows (Chesebro et al., 1982; Francis et al., 1983). Thrombin may also stimulate smooth muscle cell proliferation and synthesis of inflammatory cytokines that contribute to the

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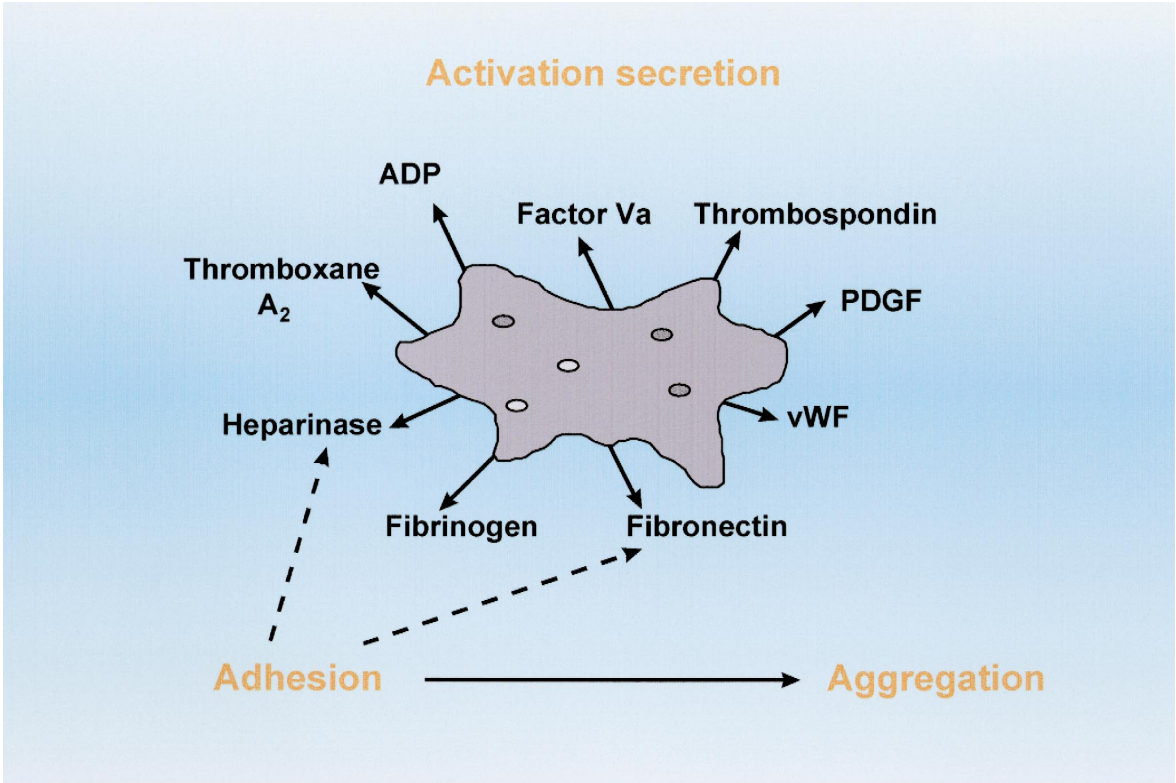

Fig. 1. Schematic presentation of the major events in primary hemostasis. The first event is platelet adhesion, the interaction of platelets with a non-platelet surface, such as vascular subendothelium. This is followed by platelet activation and secretion. Some of the products secreted by platelets are depicted. Abbreviations: ADP, adenosine diphosphate; PDGF, platelet-derived growth factor; vWF, von Willebrand's factor. The final event is the binding of activated platelets to the adherent monolayer in the process of platelet aggregation.

ongoing inflammatory process by attracting monocytes to the damaged endothelium (Flugelman et al., 1993; Wilcox, 1994). Thus, thrombin generation is most important both in the chronic progression of atherosclerotic disease and in its conversion to acute events. Evidence that thrombin is a major trigger for thrombosis in acute coronary syndromes, such as unstable angina and acute myocardial infarction, is mounting (Fuster et al., 1992). It has been shown consistently that platelets participate in the formation of thrombin through secretion of coagulation factors (Walsh and Schmaier, 1994) and by providing an anionic phospholipid surface on which the prothrombinase complex is assembled (Hawiger, 1987; Bevers et al., 1982, 1994). The source of thrombin, generation mediated by platelets (i.e., platelet procoagulant activity), has been ascribed to the rapid loss of membrane lipid asymmetry, characterized by the movement of phosphotidyl serine from the inner to the outer leaflet in a process referred to as ''membrane scrambling'' or ''flipflop mechanism'' (Sims and Wiedmer, 1991; Zhou et al., 1997). Phosphotidyl serine presentation is an essential event for the acquisition of procoagulant activity (Bevers et al., 1983), as assessed by either the conversion of prothrombin to thrombin (Rosing et al., 1980) or factor X to Xa (Van Dieijen et al., 1981) via the prothrombinase or tenase complexes, respectively. The mechanism of platelet membrane scrambling is not completely understood, but is known to be dependent on a rise in intracellular calcium concentrations (Smeets et al., 1994; Williamson et al., 1995). The thrombin-stimulated platelet glycoprotein IIb/IIIa (GP IIb/IIIa) complexes have been implicated in the process of calcium activation as assessed by electrophysiological experiments (Fujimoto et al., 1991).

3. The role of glycoprotein IIb/IIIa in platelet activation

With the disruption of the endothelial monolayer, platelet activation and adhesion to the vessel wall are promoted. Platelet activation initiates intracellular signaling that conformationally alters the major platelet membrane integrin receptor glycoprotein IIb/IIIa to create functional membrane anchors for fibrinogen and other adhesive proteins (von Willebrand factor, thrombomodulin, fibronectin, laminin, vitronectin; Nurden, 1994). The conformational changes in glycoprotein IIb/IIIa initiate intracellular signaling. Following activation of platelet suspensions by thrombin, there is a general metabolic activation within the cell viewed as a downstream event, involving G-protein dependent phopholipase C activation, generation of inositol 1,4,5-triphosphate (IP3) and diacylglycerol, protein kinase C activation, and intracellular release of cytosolic Ca^{2+} from the dense tubular system

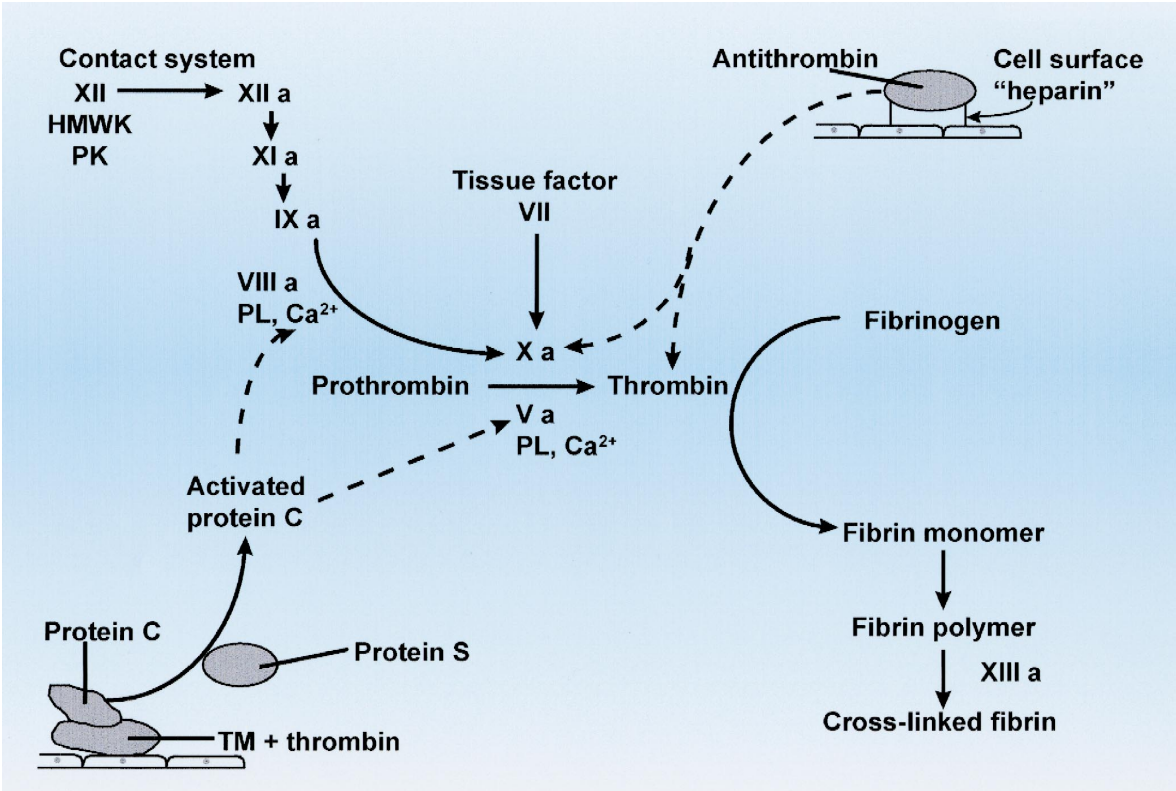

Fig. 2. A schematic diagram of some of the clinically important coagulation reactions. The unactivated or precursor proteins are indicated by roman numerals, and the active form by the addition of a lowercase ''a'' (which is a standard convention). Other abbreviations: HMWK, high-molecular-weight kininogen; PK, prekallikrein; PL, phospholipid; TM, thrombomodulin. There are two independent activation pathways, the contact system and the tissue factor-mediated or extrinsic system. They merge at the point of factor X activation and lead to the generation of thrombin, which converts fibrinogen to fibrin. These reactions are regulated by antithrombin, which forms complexes with all of the coagulation protein serine proteases except factor VII, and by the protein C-protein S system, which inactivates factor V and VIII.

(Fuster et al., 1992; Vanhoutte, 1997; Nurden, 1994). These activation processes induce the production of two potent platelet agonists: thromboxane A_2 (TxA_2) and ADP (Fig. 1). ADP and TxA_2, along with thrombin, bind to specific receptors for signaling initiation, reducing cAMP activity, inducing change of shape and activating platelet contractile elements to form irregular extending pseudopodia, and to secrete granular contents (ADP, ATP, serotonin, and Ca^{2+} from dense granules, adhesive proteins, and coagulation factors; Nurden, 1994).

4. Coronary events in acute coronary syndromes

Unstable angina occurs from reduced myocardial perfusion at rest, usually a result of thrombosis, giving rise to non-occlusive or intermittent coronary occlusion, while acute intramural myocardial infarction is almost always associated with total thrombotic occlusion of the infarct-related artery. Non-Q-wave infarction results from subtotal occlusion, or total coronary occlusion in association with collateral blood flow. Although extensive myocardial necrosis does not usually occur, unstable angina is associated with a markedly increased risk of subsequent ischemic events or myocardial infarction. Patients with non-Q-wave infarction are at higher risk of subsequent myocardial ischemia or death than patients with unstable angina (Bashour et al., 1988).

5. Aspirin — old drug with modern indications

Acetylsalicylic acid (known as aspirin), synthesized for the first time in 1897, has been widely used for pain relief, fever and inflammation, but it has also become standard therapy in acute coronary syndromes. The Second International Study of Infarct Survival (ISIS-2 collaborative group, 1988), a large, randomized, placebo-controlled, double blind trial of short-term therapy with aspirin, streptokinase, both or neither, demonstrated a 20% reduction in mortality at 5 weeks after treatment with 162.5 mg of aspirin per day. In addition, aspirin use in smaller unstable angina trials has shown a nearly 50% reduction in death and myocardial infarction (Lewis et al., 1983; Cairns et al., 1985; Theroux et al., 1988; The RISC Group, 1990).

Six randomized, double blind trials of aspirin following myocardial infarction have been conducted to evaluate the long-term efficacy of aspirin following a myocardial infarction (Elwood et al., 1974; The Coronary Drug Project

Research Group, 1976; Breddin et al., 1980; Elwood and Sweetnam, 1979; The Persantine-Aspirin Reinfarction Study Research Group, 1980; Aspirin Myocardial Infarction Study Research Group, 1980). The trials used aspirin doses ranging from 300 to 1500 mg daily and the study duration varied from 1 to 4 years. No clear benefit of therapy was shown, although five of the six showed trends for reduction of all-cause mortality. In fact, the Aspirin Myocardial Infarction Study Research Group, as late as 1980, observed a trend against aspirin for mortality (Aspirin Myocardial Infarction Study Research Group, 1980). Today, it has become clear that these studies were limited by an insufficient sample size. In 1994, the Antiplatelet Trialists' Collaboration performed a meta-analysis of 145 randomized trials of prolonged anti-platelet therapy with either aspirin, dipyridamole and aspirin, sulfinpyrazone, or ticlopidine (Antiplatelet Trialists' Collaboration, 1994). The conclusion was that platelet inhibitors were beneficial in coronary artery disease. Significant reductions were noted in vascular mortality (13%) and nonfatal reinfarction (31%). The most extensively studied and best documented antiplatelet regimen was aspirin. Despite such promise, aspirin is a weak platelet inhibitor and significant morbidity and mortality still exists even with aspirin therapy.

6. Vitamin K antagonists in coronary artery disease

Anticoagulation has been identified as an important contributor to reducing cardiovascular complications after acute myocardial infarction. Due to the fast action of heparin as anticoagulant and the restricted need during the first few days only of an attack of unstable coronary artery disease, there has been no role of oral anticoagulation using vitamin K antagonists (Warfarin, etc.) in acute coronary syndromes. In chronic therapy, i.e., secondary prevention, however, a number of studies have assessed the safety and efficacy of oral anticoagulation in patients after myocardial infarction (Asinger et al., 1981; Drapkin and Merskey, 1972; Wasserman et al., 1966; Loeliger and Hemker, 1967; Meuwissen et al., 1969; Soerensen et al., 1969; The Sixty Plus Reinfarction Study Research Group, 1980; Smith et al., 1990). The Warfarin Re-Infarction Study (WARIS, 1990) clearly demonstrated a benefit in terms of total mortality (a risk reduction of 24%), reinfarction (a reduction of 35%) and stroke (a reduction of 55%). This was confirmed by the ASPECT trial (The ASPECT Research Group, 1994). Only one short-term and two long-term trials have compared the use of aspirin and oral anticoagulants directly against each other. All were designed and conducted in an unblinded fashion (Breddin et al., 1980; The EPSIM Research Group, 1982; Julian et al., 1996). There was no statistically significant difference between the groups, neither for endpoint mortality nor for reinfarction. The upcoming WARIS-II trial will provide further answers as to the role of oral anticoagulation in coronary heart disease.

7. Heparin in acute ischemic syndromes

Several studies have shown that both tissue factor and tissue factor pathway inhibitor levels are increased in plasma of patients with ischemic heart disease, particularly in unstable angina (Neri Serneri et al., 1992; Sandset et al., 1989; Neri Serneri et al., 1990a,b). However, elevated plasma levels of tissue factor are not sufficiently balanced by high tissue factor pathway inhibitor levels, and this disbalance is associated with the hypercoagulability observed (Falsiani et al., 1998). The ability of heparin in reducing tissue factor mRNA expression in monocytes (Peoe et al., 1997) and releasing tissue factor pathway inhibitor (Sandset et al., 1988) may have a role in decreasing hypercoagulability in patients with ischemic heart disease. Four studies have consistently shown that the combination of heparin infusion and aspirin results in a reduction in the risk of death or myocardial infarction of approximately 65% in comparison with aspirin, without increasing the risk of major bleeding complications (Theroux et al., 1988; The RISC Group, 1990; Theroux et al., 1993; Cohen et al., 1994).

Therefore, intravenous heparin has become a recommended therapy in the treatment of patients with acute coronary syndromes (Mark and Braunwald, 1995; Verstraete et al., 1995). This is supported by further findings that heparin leads to an improved clinical outcome in patients with unstable angina (Telford and Wilson, 1981) and myocardial infarction (SCATI Group, 1989). The anticoagulant action of heparin is primarily due to its ability to bind tightly to antithrombin-III, thereby accelerating the rate of inhibition of major coagulation enzymes, particularly thrombin, and to a lesser extent, activated factors X, IX, XI and XII (Fig. 2; Barrowcliffe and Thomas, 1983; Rosenberg, 1975). Biochemical studies in patients with acute coronary syndromes have clearly demonstrated that intravenous heparin rapidly inhibits thrombin–fibrinogen interactions and lowers plasma fibrinopeptide A levels to within the normal range (Mombelli et al., 1984; Gallino et al., 1986; Neri Serneri et al., 1990a,b). It is well established that prothrombin fragment $1 + 2$ (a marker of thrombin generation) is elevated in the acute phase of unstable angina (Kienast et al., 1993) and myocardial infarction (Szczeklik et al., 1992). It has been shown that intravenous heparin, given at doses capable of reducing plasma fibrinopeptide A levels in the majority of the patients with acute coronary syndromes, does not reduce plasma prothrombin fragment $1 + 2$ levels (Merlini et al., 1997). The absence of any effect of heparin on thrombin generation in particular may be due to the fact that factor Xa bound to activated platelets is protected against inactivation by the heparin–antithrombin complex (Teitel and Rosenberg, 1983). Indeed, there is evidence for a better inactivation of factor Xa by heparin–antithrombin complexes compared with thrombin. Recently, investigators have identified a clustering of thrombotic events after the

abrupt cessation of heparin and other thrombin inhibitors (Theroux et al., 1992; Gold et al., 1993), which suggests that the benefits of anti-thrombin therapy may be limited by a reactivation of thrombosis after its discontinuation. A possible mechanism suggested by Gold et al. (1993) was a reduction of thrombin available to form thrombin–thrombomodulin complex, resulting in reduced activation of the natural anticoagulant protein C.

Thus, the value of intravenous heparin (in addition to aspirin) in protecting patients with unstable coronary artery disease from recurrence of symptoms and progression to myocardial infarction or death is well established. Heparin should be considered for use in all patients, but must be carefully monitored with frequent measurement of the activated partial thromboplastin time (APTT), because of the variability in patient response, complex pharmacokinetics, and the acknowledged risk of hemorrhage.

8. Unfractioned versus LMWH (low-molecular-weight-heparins)

Several other mechanisms have been proposed for a rebound increase in thrombin activity after discontinuing heparin or other antithrombin agents (Amiral et al., 1989; Willerson and Casscells, 1993; Marciniak and Gockerman, 1997). The general mechanism may involve an accumulation of prothrombotic factors when thrombin is inhibited, which results in a transient hypercoagulable state upon discontinuation of the therapy. A gradual discontinuation of heparin therapy by switching from intravenous to subcutaneous heparin is suggested as a possible means to reduce the risk of rebound (Braunwald et al., 1994). The LMWHs represent a significant advance in anti-thrombotic therapy. They have pharmacological and pharmacokinetic advantages over standard heparin resulting in potentially greater efficacy and safety profile (Hirsh and Levine, 1992): they have a highly predictable dose–response curve, which means they can be used without APTT monitoring. Growing clinical evidence suggests that LMWHs will play an important role in the management of unstable angina, with improved efficacy and lower risk of bleeding complications, compared with standard heparin. For instance, LMWH significantly reduced the risk of acute myocardial infarction compared with aspirin alone or a combination of aspirin and standard heparin in patients with unstable angina in a study by Gurfinkel et al. (1995). In the FRISC study, the LMWH dalteparin reduced the risk of death of myocardial infarction by 63% as compared to placebo (FRISC study group, 1996). Furthermore, it has recently been shown that continuing treatment with dalteparin for a total of 6 weeks further reduces the rate of death or myocardial infarction from 10.9% to 7.4% (RR 0.67; confidence index 0.31–1.44) in high-risk patients who have elevated levels of troponin-T during the acute phase (Lindahl et al., 1997); no other interventions have yet been shown to offer similar benefits to these patients.

9. Thrombolysis

Thrombolytic therapy has been shown to reduce mortality following myocardial infarction dramatically, and its success is largely due to early recanalization of the obstructed artery (GISSI, 1987; ISIS 2 collaborative group, 1988; GISSI-2, 1990; ISIS-3 collaborative group, 1992; The GUSTO investigators, 1993). The effect of coronary thrombolysis is potentiated by acetylsalicylic acid (ISIS 2 collaborative group, 1988), and platelet glycoprotein IIb/IIIa (GPIIb/IIIa) blockers (Ohman et al., 1997). Conjunctive heparin treatment has not been shown to improve prognosis in patients receiving non-fibrin specific thrombolytic agents (GISSI-2, 1990; ISIS-3 collaborative group, 1992; The GUSTO investigators, 1993). During thrombolytic therapy, fibrin-adsorbed thrombin is released (Bloomal, 1962), and increased thrombin activity has been demonstrated (Seitz et al., 1988). Platelets (Rasmanis et al., 1992), factor V (Lee and Mann, 1989) and protein C (Varadi et al., 1992; Gruber et al., 1993) are also activated during thrombolytic therapy.

10. Hirudin — a direct thrombin inhibitor

In vitro studies indicated that fibrin bound thrombin is susceptible to inactivation by antithrombin III independent inhibitors, such as hirudin (Stone and Hofsteenge, 1986). Hirudin is an irreversible inhibitor of thrombin, and requires no cofactor for its anticoagulant action (Lindhot et al., 1990). Hirudin is an effective inhibitor of clot bound thrombin, whereas heparin inhibits predominantly soluble thrombin (Weitz et al., 1990). A study by Rao et al. (1996) has shown that hirudin manifests its ability to inhibit clot bound thrombin in vivo. Hirudin is more effective in inhibiting thrombin action and fibrin formation, but not thrombin generation, even at relatively high levels of anticoagulation. Hirudin has a relatively smaller effect than heparin in inhibiting continued thrombin generation. Hirudin does not inactivate factor Xa, which can effectively activate factors V and VIII when the proteolytic action of thrombin is blocked (Weitz et al., 1990; Rao et al., 1996). Factors Va and VIIIa play an important role in continued thrombin generation (Fig. 2). In contrast, heparin is an effective inhibitor of factor Xa (Ofosu et al., 1987, 1989). Patients receiving hirudin at the lowest dose had higher levels of plasma fibrinopeptide A and prothrombin fragment $1 + 2$ than patients treated with higher hirudin doses and heparin. The lowest dose assessed appears inadequate for use of hirudin alone as an antithrombotic agent (Rao et al., 1996). Nevertheless, because of these demonstrated differences, there may be a role for

both classes of thrombin inhibitors in the appropriate clinical scenario.

11. Inhibition of thrombin generation by glycoprotein IIb/IIIa receptor antagonists

Recently, it has been shown that thrombin generation initiated by tissue factor in the presence of platelets was significantly inhibited by chimeric c7E3 Fab antibody (Reverter et al., 1996), a glycoprotein IIb/IIIa receptor antagonist. However, it is well known that c7E3 Fab is not a selective inhibitor of fibrinogen binding to the glycoprotein IIb/IIIa complex, but also interferes at the level of the vitronectin receptor and Mac-1 complexes (Simon et al., 1997). Platelet surface receptors are known to participate in the activation of the coagulation system through binding of coagulation factors, such as factor Xa (Altieri and Edgington, 1988; Altieri et al., 1988). It has been reported that complete blockade of glycoprotein IIb/IIIa by c7E3 Fab could only reduce thrombin generation by 45–50% (Reverter et al., 1996). Another compound, SR121566A, a new non-peptide glycoprotein IIb/IIIa inhibitor with high affinity for the glycoprotein IIb/IIIa complex, has been synthesized (Savi et al., 1998). SR 121566A revealed a high level of selectivity for glycoprotein IIb/IIIa with regard to other glycoproteins, such as vitronectin, exhibited potent inhibition of human and rabbit platelet aggregation and strong antithrombotic activity in this species (Hoffmann et al., 1998). It has been shown that SR 121566A inhibits thrombin generation at concentrations which also strongly reduced ADP, arachidonic acid, or collagen-induced platelet aggregation. This compound could reduce thrombin generation by 72% (Herault et al., 1998).

The initial studies of parenteral glycoprotein IIb/IIIa inhibitors in acute coronary syndromes have shown that adverse clinical events and subsequent morbidity can indeed be reduced with these agents (The PURSUIT Trial Investigators, 1998; The PRISM-PLUS Study Investigators, 1998). Drugs, such as abciximab and eptifibatide, produced profound ex vivo inhibition of platelet function as determined by conventional aggregometry ($>80\%$) in studies of patients with ongoing acute thrombotic events, i.e., platelet aggregates had already formed in the setting of unstable angina and acute myocardial infarction. Particularly, several clinical trials (The EPIC Investigators, 1994; The EPILOG Investigators, 1997; The CAPTURE Investigators, 1997; The RESTORE Investigators, 1997; The impact II investigators, 1997; Kong et al., 1998) have demonstrated that intravenous glycoprotein IIb/IIIa inhibitors reduce rates of death, myocardial infarction, and the need for acute revascularization by about one-third in patients undergoing percutaneous revascularization. Also, four trials (The PARAGON Investigators, 1998; The PURSUIT Trial Investigators, 1998; The PRISM-PLUS Study Investigators, 1998; The PRISM Study Investigators, 1998) with three small-molecule glycoprotein IIb/IIIa inhibitors explored the role of these drugs in the primary management of non-ST-segment elevation acute coronary syndromes. Collectively, these studies suggest that significant improvements in the outcomes of patients with non-ST-segment elevation acute coronary syndromes can be achieved through the addition of intravenous glycoprotein IIb/IIIa inhibitors to a regimen of aspirin and heparin. Such data definitely supports the role of intravenous glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. Yet, despite the reported profound degree of ex vivo platelet inhibition, adverse clinical events still occurred. This observation raised two important questions: first, did enough glycoprotein IIb/IIIa inhibition occur in the patients with adverse thrombotic events, and second, is the IIb/IIIa receptor indeed the final and only primary receptor of importance, or should other adhesive molecules involved in platelet–platelet and platelet–neutrophil interactions be considered and targeted? Both questions are to date still unanswered.

The initial benefits of acute parenteral glycoprotein IIb/IIIa inhibitors have stimulated the interest in clinical trials with oral agents. Yet, thus far, the positive evidence for benefit is less than overwhelming. To date, while platelets indeed were inhibited in ex vivo turbidometric assays, there are no data to support clinical efficacy with oral IIb/IIIa inhibitors. The reduction in clinical adverse outcomes with xemilofiban in the ORBIT trial (Kereiakes et al., 1998) did not hold up in the phase III EXCITE trial (Chew et al., 2000). Similar disappointing results were observed in the SYMPHONY trial with sibrafiban, and with orbofiban in the prematurely cancelled OPUS-TIMI 16 trial (The SYMPHONY Investigators, 2000; Chew et al., 2000). Moreover, a pooled analysis of these large-scale trials suggests an increased mortality with long-term use of these agents (Chew et al., 2000). In addition, increased bleeding events are constantly observed in the patients receiving oral glycoprotein IIb/IIIa antagonists. Representative for these trials of oral glycoprotein IIb/IIIa inhibitors, the above-mentioned SYMPHONY trial (2000), shall be presented here in more detail: in this study, it was investigated whether sibrafiban (a glycoprotein IIb/IIIa inhibitor) would prevent more cardiovascular events than aspirin. The investigators randomly assigned 9233 patients stabilized after an acute coronary syndrome to either aspirin (80 mg orally twice daily) or sibrafiban at various doses (3.0, 4.5 or 6.0 mg daily). The drugs were given within 7 days of, and sustained for 90 days after, an acute coronary syndrome event. The primary endpoints (composite of death, non-fatal infarction or reinfarction, or severe recurrent ischemia at 90 days) were not significantly different between the groups assigned to aspirin (302 (9.8%)), low-dose sibrafiban (310 (10.1%); odds ratio 1.03 (95% CI 0.87–1.21)), and high-dose sibrafiban (303 (10.1%); 1.03 (0.87–1.21)). The groups did not differ

significantly in the rates of component events either. However, major bleeding was more common with high-dose sibrafiban (171 (5.7%)) than with aspirin (120 (3.9%)) or low-dose sibrafiban (159 (5.2%)). Thus, no significant advantage of sibrafiban over aspirin was observed.

12. Increased thrombin generation in congestive heart failure

Taking the issue of thrombin generation in coronary artery disease to congestive heart failure is a logical conceptual expansion, as most patients with congestive heart failure represent late stage coronary artery disease after having suffered from myocardial infarction in the past. Few clinical studies, however, have been performed to determine thrombin generation in patients with congestive heart failure. Few experimental and clinical studies describe impaired endothelium-dependent vasodilatation and impaired plasma concentration of endothelin and nitric oxide, which could potentially affect generation of thrombin in congestive heart failure patients (Vanhoutte, 1996). Soncini et al. (1997) conducted a study in 64 patients with congestive heart failure, half of them with chronic atrial fibrillation. Patients were also stratified according to a history of prior stroke. The generation of thrombin was measured by means of molecular markers of prothrombin fragment 1 + 2 and thrombin–antithrombin III complex. This trial showed that levels of prothrombin fragment 1 + 2 were higher in congestive heart failure patients with atrial fibrillation and stroke, than in those without stroke, revealing that there is a true clotting activation in these subjects. High plasma levels of prothrombin fragment 1 + 2, fibrinopeptide A and thrombin–antithrombin complexes have been consistently observed in patients with decompensated heart failure undergoing cardiac transplantation (Livingstone et al., 1996). Moreover, post-myocardial infarction patients with heart failure exhibited significantly higher mean thrombin–antithrombin III and fibrinopeptide A levels on days 3, 5, and 7 of the coronary event when compared with patients in whom heart failure was absent (Szczeklik et al., 1992). Further investigation of pathophysiology and diagnostic utility of thrombin generation in patients with congestive heart failure is warranted.

13. Conclusion

In conclusion, coronary artery thrombosis, superimposed on a disrupted atherosclerotic plaque, has emerged as the pivotal pathophysiological event in acute coronary syndromes, including unstable angina, acute myocardial infarction and sudden death. Since thrombin generation is key in the pathogenesis of thrombosis, recent studies have focused on thrombin inhibition in the management of acute ischemia. Heparin is the most widely used anticoagulant for acute management of thrombosis. Combined treatment with aspirin and heparin has proved more efficacious than either treatment alone in the risk reduction of serious cardiac events in patients with unstable angina or non-Q-wave infarction. LMWHs are significantly superior to standard heparin in reducing the composite frequency of death, myocardial infarction and recurrent angina. Although these novel LMWHs overcome many of the pharmacokinetic limitations of standard heparin, both low molecular and unfractioned heparin are relatively ineffective inhibitors of clot bound thrombin: when thrombin binds to fibrin, it remains enzymatically active and relatively impervious to inactivation by heparin. In contrast to heparin, direct thrombin inhibitors, such as hirudin, inhibit free and clot bound thrombin equally well, because their sites of interaction are not masked when thrombin binds to fibrin. Recently, it has been shown that glycoprotein IIb/IIIa antagonists inhibit thrombin generation at concentrations which also strongly reduced ADP-, arachidonic acid- or collagen-induced platelet aggregation. Increased thrombin generation and thrombin activity have also been observed in patients with congestive heart failure. Despite the importance of thrombin in both the chronic progression of atherosclerotic disease and in its conversion to acute events, the diagnostic utility of the early determination of thrombin generation markers in patients with acute coronary syndromes remains to be elucidated. Further investigation of therapeutic modifications of thrombin generation appears warranted, particularly in patients with heart failure and in the chest pain population.

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