Thrombolysis in acute myocardial infarction
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Chapter IV

Early and late reocclusion in patients with myocardial infarction

1. Introduction

Following thrombolytic therapy, occluded infarct related coronary arteries can be reperfused as a result of plasminogen activation. Coronary angiography is the golden standard for its detection. The speed of reperfusion is, among other variables, dependent on the type of thrombolytic agent which is administered. Therapy with rt-PA dissolved a clot quicker compared to infusion of SK (TIMI,1985) although 3 to 4 hours after initiation of therapy reperfusion rates became similar (Ganz,1992; GUSTO Angiographic Investigators,1993). This has been called the "catch-up" phenomenon of infarct vessel patency. Very early reperfusion might be intermittent (Hackett,1987; Krucoff 1990,1993; Kwon,1991). In this phase it is not qualified as reocclusion. Persistent early reocclusion is often accompanied by clinical symptoms and electrocardiographic signs. Since a relation between early reocclusion and increased in-hospital mortality has been demonstrated (Ohman,1990), its occurrence will be of clinical relevance.

2. Occurrence and mechanism

Quantification of the reocclusion rate will require repeated coronary angiography. After combining the results of randomized trials in which rt-PA plus i.v. heparin was compared with non-fibrin specific thrombolytic agents, reocclusion rates, determined after several days or before discharge, were 13.5 and 8% (p=0.002), respectively (Granger,1992). When anistreplase was used, reocclusion after 24 hours was found in only 4% of the patients (Relik-van Wely,1991). This low figure is comparable to our results as no reocclusion occurred between 1½ and 48 hours after therapy with anistreplase (appendix 8). Reocclusion 3 months after initial successful thrombolytic therapy with SK or anistreplase was found in about 30 and 28% of the patients in the APRICOT study and our study, respectively (Meijer,1993; appendix 8). Patients in the APRICOT study with persistent patency at coronary angiography after 3 months showed a slight increase in left ventricular ejection fraction (LVEF), those with reocclusion did not. Their finding of an absence of further LVEF deterioration despite reocclusion corresponds with ours. Presence, or even enhanced, development of collateral blood flow might have been responsible for the stabilization of LVEF in these patients.

Early after reperfusion the stimulus for rethrombosis is strongest because of a) re-exposure of the cracked plaque, b) hypercoagulability and activation of platelets induced by thrombolytic therapy (see below), and c) the presence of locally vasoactive substances released by activated platelets. Thus, early reocclusion (within hours or days) may be related to other mechanisms than reocclusion after weeks or months (late). In late reocclusion lesion remodelling due to endothelial growth may be of primary importance. In contrast to early reocclusion, late reocclusion often occurs silently (Ohman,1990; appendix 8). Actually, the precise course of events leading to late reocclusion is less well understood than of those leading to early reocclusion.
3. Factors determining reocclusion

Thrombolytic agents convert plasminogen to plasmin. Presence of plasmin in the circulation leads to fibrinogenolysis, loss of activity coagulation factors V and VIII, and the accumulation of fibrinogen degradation products. These effects impair blood coagulability. In addition, membrane glycoproteins at the platelet surface are degraded by plasmin, which may result in impaired adhesion and aggregation of platelets. Thus, initially, a state of hypocoagulability and platelet dysfunction will occur. However, abundance of free plasmin or the binding of anti-SK antibodies to the SK-plasminogen complex located at the platelet surface, may trigger processes leading to platelet activation and hypercoagulability (Vaughan 1988,1991; Sherry,1992a).

Activated platelets release thromboxane A2. This peptide strongly supports platelet aggregation. During thrombolytic therapy with either rt-PA or SK, a striking increase of thromboxane A2 metabolites in plasma and urine has been measured (Fitzgerald,1988; Kerins,1989). Therefore it is believed that marked platelet activation takes place following thrombolytic therapy.

The paradoxical hypercoagulable state in patients with MI after thrombolytic therapy with either SK or rt-PA is illustrated by the presence of clearly elevated fibrinopeptide A (FPA) levels in their plasma (Eisenberg 1986,1989; Owen,1988). As mentioned in the 5th paragraph of the former chapter, no relation between reperfusion and FPA levels has been demonstrated. With regard to reocclusion, in patients treated with heparin in conjunction to thrombolytic therapy, an FPA threshold level of 50 ng/ml 24 hours following thrombolysis, appeared to be a relative specific marker of subsequent vessel occlusion (86%), but lacked sensitivity (48%) (Rapold,1992).

When reperfusion of an occluded vessel has been achieved, the balance between prothrombotic and anti-thrombotic factors will determine the incidence of early reocclusion. Of importance are a) severity and geometry of the underlying coronary artery stenosis, b) presence of residual coronary arterial thrombosis, c) platelet adhesiveness and aggregation potential, d) rheologic parameters like flow properties, shear stress, fibrinogen content and, possibly, e) fibrin(-ogen) degradation products which express anticoagulant activity, and f) anticoagulant and/or antiplatelet therapy (Latallo,1964; Marder,1969; Haverkate,1979; Harrison,1984; Gash,1986; Adams,1987; Moriarty,1988; Davies,1991; Hoffmannn,1993).

4. Traditional ways to prevent reocclusion

It has been suggested that the presence of a high-grade residual stenosis at coronary angiography after successful thrombolysis may predict recurrent ischemia (Harrison,1984; Gash,1986). Subsequently, several well designed studies were performed to assess the hypothesized additional benefit of early coronary angioplasty (PTCA) after thrombolytic therapy because of MI (Topol and the TAMI Group,1987; TIMI,1988; Simoons,1988). These trials showed that thrombolytic therapy combined with immediate PTCA did not appear to be superior to early non-invasive treatment using i.v. rt-PA, heparin and acetylsalicylic acid. In contrast, a complicated clinical course occurred more frequently and mortality may be higher due to an early invasive strategy. Recently, the APRICOT-investigators studied the relation between angiographic reocclusion at 3-months and
residual stenosis after successful thrombolysis (Veen, 1993). They showed that stenosis severity exceeding 90% was a significant independent predictor for reocclusion. One might object that the APRICOT findings appears in contrast to the results of the TAMI group. However, the TAMI study focussed at recurrent ischemia before hospital discharge, not at reocclusion (Ellis, 1989).

The severity of the underlying ruptured coronary lesion cannot be influenced by systemic thrombolytic therapy, this in contrast to the mechanical approach by PTCA. In skillful hands, this procedure, without previous thrombolytic therapy, was recently shown to be superior in patients with MI compared to i.v. SK therapy with respect to patency rate, residual left ventricular function, and incidence of recurrent myocardial ischemia (Zijlstra, 1993).

In the course of complete clot digestion by thrombolytic treatment, residual coronary thrombus is present. This material is a particularly long lasting thrombogenic substrate, even more thrombogenic than deeply injured arterial tissue (Badimon 1988, 1991). Persistent exposure of thrombin may be a predisposing factor both to initial failure of recanalization and to early reocclusion.

The most widely used antithrombotic agent is heparin (Hirsh, 1991). Following its use in patients with MI, plasma FPA level decreased indicating its antithrombin effect (Gallino, 1986). Heparin was given subcutaneously 12 hours after the thrombolytic agent in the GISSI-2 study. This regimen was disapproved because the delay was qualified as too long to prevent reperfused coronary arteries from reocclusion. Meeting the critics, in ISIS-3 subcutaneous administration of heparin was started 4 hours after thrombolytic therapy. However, as was indicated by only minimal extension of the activated partial thromboplastin time (aPTT), the degree of anticoagulation was definitely not in the therapeutic range (Kroon, 1992; Delanty, 1992; Goldhaber, 1992). It appeared that specific questions like the usefulness of heparin and its optimal mode of administration, were more adequately answered in small, but well designed and conducted trials. Such trials demonstrated that in patients with MI treated with rt-PA, i.v. heparin is of superior efficacy compared to placebo or aspirin in obtaining patency of the infarct related vessel (Bleich, 1990; Hsia, 1990; de Bono, 1992). Moreover, the quality of heparinization, as measured by the degree of prolongation of the aPTT, has been related with a more beneficial outcome (Hsia, 1992; Arnout, 1992). Thus, when heparin is given in patients with MI, measurement and appropriate adjustment of the dosage guided by the aPTT are of major importance. Currently, only in a minority of patients aPTTs two to three times the control values were obtained during several days in various studies (Hsia, 1992; Becker, 1993).

An oral dose of 325 mg aspirin blunted the increase of thromboxane A2 metabolites in patients with MI treated with rt-PA or SK (Fitzgerald, 1988; Kerins, 1989). This finding, among others, provided a rationale for adjunctive antiplatelet therapy to thrombolytic therapy (Stein, 1989; Winters, 1991). After performing a meta-analysis, it has been stated that aspirin in the presence of heparin significantly reduced the incidence of coronary reocclusion and recurrent ischemia after thrombolysis with either SK or rt-PA (Roux, 1992). Criticizers, however, rebutted that the multiplicity of individual study designs did not allow such a conclusion (Sherry, 1992b; Ridker, 1993).

With respect to late reocclusion and recurrent MI, it has been attempted to prevent this
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with coumadin treatment. However, the APRICOT-study showed that the reocclusion rate in patients who used either aspirin, coumadin or placebo was similar at angiography after 3 months (Meijer, 1993). Interestingly, in that study treatment with aspirin was associated with a significantly lower incidence of reinfarction compared to placebo.

5. New ways to prevent reocclusion

Given the overall poor quality of anticoagulation using i.v. heparin, one may attempt to speed up aPTT or activated clotting time (ACT) measurements and perform these tests at the bedside. Probably this might improve the efficacy of treatment (Ogilby, 1989; Ansell, 1991; Vacek, 1991; Melandri, 1993; Grill, 1993).

Because residual anchored mural thrombus contains active thrombin, adsorbed to deeper lying layers of fibrin, it is poorly accessible to the large heparin-antithrombin III complex (Liu, 1979; Bar-Shavit, 1989; Hogg, 1989; Weitz, 1990). Thus, more effective antithrombin agents may be needed. These agents, named argatroban and hirudin, are currently studied (Fitzgerald, 1989; Jang, 1990; Clarke, 1991; Gold, 1993). Hirudin, a small peptide derived from the pharyngeal glands of the leech was recently manufactured using a recombinant technique. It is the most potent and selective inhibitor of thrombin currently known. Unlike heparin, hirudin does not require any endogenous cofactor such as antithrombin III for its anticoagulant effects (Hoet, 1991; Deutsch, 1993). In contrast to heparin, hirudin neutralizes fibrin-bound thrombin (Mirshahi, 1989) and does not increase platelet adhesion to fibrin (Verstraete, 1992). Two human pilot-studies showed hirudin, compared to heparin, to be as effective, or even more so, in preventing reocclusion after successful thrombolysis, without any safety problems (Neuhaus, 1993; Cannon, 1993). Careful dose-ranging studies followed by large randomized controlled trials will be required to establish to what extent the ratio of anti-thrombotic efficacy to bleeding risk differs from that of conventional therapy (Anonymous, 1992).

When platelets are activated, the glycoprotein IIb/IIIa (GPIIb/IIIa) complex at the platelets’ surface plays a prominent role in the binding of fibrinogen and other ligands (Coller, 1990). Specific inhibition of this complex in vitro and in vivo was shown to be possible with a monoclonal antibody named 7E3 [7E3-(F(ab')2]. After its administration, there was profound inhibition of platelet function, leading to acceleration of thrombolysis with rt-PA and prevention of reocclusion (Coller, 1985; Gold, 1988). The clinical efficacy and safety of these antibodies as therapeutic agents are currently under investigation (Gold, 1989; Kleiman, 1993).

6. Conclusions

Mechanisms involved in early and late reocclusion are probably different. Early reocclusion appears related to factors such as hypercoagulability and platelet activation, which may paradoxically follow thrombolytic therapy. Exposure of the denuded cracked coronary plaque or, in particular, residual mural thrombus, serves as a thrombogenic substrate. In addition, the extent of early reperfusion may also be important with regard to early reocclusion: TIMI grade 2 flow (partial perfusion) may no longer be perceived as equal to TIMI grade 3 flow (complete perfusion) since patients with TIMI grade 2 flow
have enzymatic, electrocardiographic and pump function indices of MI similar to those of patients with grade 0 or 1 flow (no or minimal perfusion) (Karagounis, 1992; Anderson, 1993).

Factors involved in late reocclusion have been identified as severity and surface geometry of the residual stenosis (Veen, 1993). Rheologic factors may play an additional role. Late reocclusion, although occurring relatively frequently, is not necessarily accompanied by symptoms or deterioration of myocardial function.

Optimal reperfusion characterized by rapid (within 60-minutes), complete (TIMI grade 3 flow) and sustained coronary recanalization with adequate myocardial tissue perfusion (absence of the "no-reflow" phenomenon) and absence of reocclusion, is only achieved in 25% or less of the patients with MI treated with thrombolytic agents (Lincoff, 1993).

Currently adjunctive and/or conjunctive therapy to thrombolysis with new antithrombin or platelet inhibiting agents appear a most promising area of which additional therapeutic benefits could be expected in the near future.