Thrombolysis in acute myocardial infarction
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Chapter III

Significance of coagulation parameters in the outcome of thrombolytic therapy

1. Introduction

In the early days of thrombolytic treatment SK was the only agent used. Therapy was guided under the assumption that SK-inhibitory constituents in the patients’ plasma had to be overruled before any local effect of therapy could be expected. Assessment of SK-inhibitory constituents in the patients’ plasma was done by use of the "predicted dose test" (Johnson, 1957). On the basis of this method patients received an i.v. loading dose varying from 35,000 to 1,500,000 U SK (Fletcher, 1959). In those days, clinicians considered anti-streptokinase antibodies (aSKa) to be the origin of SK-resistance. Former human streptococcal infections were supposed to have elicited antibodies in the plasma which crossreacted with SK. In the 1960s, when thrombolytic therapy was administered on a limited scale, clinicians used a modification of the "predicted dose test", the "titrated initial dose" test, to determine the loading dose of SK necessary to induce a systemic lytic state. Applied dosages varied between 25,000 and 3,000,000 U (Verstraete, 1966). This corresponded with an interindividual variation in dosage of over a 100-fold range. The loading dose was below 1,250,000 U SK in 97% of the patients. Subsequently, a maintenance dosage of 100,000 U SK per hour was given in order to keep fibrinogen and plasminogen low during several days of treatment.

SK-resistance was described in several studies in the 1970s. It was reported that 32 of 236 blood donors (15.6%) would have required a loading dose of SK exceeding 250,000 U to overcome resistance to treatment with SK (James, 1973). In 312 patients in whom the "titrated initial dose" test was performed, it was found that 7% of them had a SK-resistance exceeding 250,000 U (Arnesen, 1977). A recent streptococcal infection in patients was associated with a significantly higher SK resistance. Patients, who had an antistreptolysin titre (AST) exceeding 625 U showed a greater SK resistance compared to patients who had an AST under 125 U (Aznar, 1976). Very high levels of IgG to SK were not found in a recent small study (Buchalter, 1992). Thus, the reported incidence of aSKa is subject to variability.

2. Systemic lytic state and anti-streptokinase antibodies (aSKa)

In the 1980s it was demonstrated that a systemic lytic state, defined as a certain decrease in fibrinogen after thrombolytic therapy, was associated with success of SK therapy (Rothbard, 1985; Six, 1987). On the other hand, a non-systemic lytic state in patients who were treated with anistreplase was associated with non-patency (Marder, 1987). In our study this finding was confirmed; all patients with MI showing a systemic non-lytic state, defined as fibrinogen in excess of 1 g/l, turned out to have non-patency of the infarct related vessel after treatment with anistreplase (appendix 2). It has
been suggested that aSKa might be responsible for the absence of a systemic lytic state but at the time of this study aSKa could not be measured. Following completion of the assay (appendix 3), we found that a systemic non-lytic state in patients could be explained by the presence of high levels of aSKa (appendix 4). However, the occurrence of a systemic lytic state after anistreplase administration was not absolutely predictive for success of therapy. In fact, despite a lytic state, 17% (9/52 patients) showed a non-patent infarct related vessel. It is therefore likely that other local or systemic antifibrinolytic factors, such as Lp(a) and/or PAI, may also be involved.

In contrast to our data, another study, in which the pretreatment aSKa levels of 333 patients were measured, reported no correlation between aSKa and patency after anistreplase therapy (Fears, 1992). These investigators used a radio-immuno assay (RIA), whereas we used an enzyme-linked immunosorbent assay (ELISA). Until now, these 2 assay techniques have not been compared with each other.

2.1. Determination of anti-streptokinase antibodies (aSKa)

Variants of Johnson’s "predicted dose test", such as the "titrated initial dose test", the "streptokinase-resistenz-test" and the "streptokinase reactivity test" have been used for determination of the appropriate dosage in patients with thromboembolic disease (Deutsch, 1960; Amery, 1963). In 1983, a specific ELISA for quantitative assessment of aSKa has been described (Leonardi, 1983), but no reports on its use emerged. The aSKa assay using a RIA (Moran, 1984) was used more often. However, this method is time consuming which disqualifies its application for immediate clinical practice purposes. A quick aSKa level determination offers the opportunity to administer complementary or alternative thrombolytic therapy when titers are high. This strategy may thus render clinical benefits in the first phase of MI (Sigwart, 1985; appendix 5). So far, no studies have been published which described pre-thrombolysis blood sampling, immediate assessment of aSKa and subsequently adaptation of the dosage of SK and/or adjunctive rt-PA infusion in case of a high aSKa titre. Because of its delayed assessment, aSKa determination has never become popular. As a surrogate parameter, some clinicians routinely measured serum fibrinogen immediately after administration of SK in order to identify patients in whom delayed or failed reperfusion is likely to be due to a high aSKa titer (Lew, 1985b). As we illustrated in appendix 2, this appears to be a rational approach to detect failure of anistreplase (and probably SK). Now that a rapid and easy to perform assay has been developed (appendix 3), its clinical benefit needs to be determined.

3. Role of plasminogen activator inhibitor (PAI)

Endogenous tissue-plasminogen activator (t-PA) is a serine protease which converts plasminogen to plasmin. It is localized in endothelial cells and released into the blood in response to a variety of stimuli like thrombin formation, fibrin deposition, ischemia, stress, physical exercise or venous occlusion. The concentration of t-PA antigen in plasma is about 3.8-4.5 ng/ml (Angleton, 1989). Its activity is regulated by the inhibitor plasminogen activator inhibitor (PAI) of which two forms are known: PAI type 1 (PAI-1) and PAI type 2. The latter is found in pregnancy and not of relevance in MI. PAI-1, further referred to
as PAI, is one of the main inhibitors of endogenous fibrinolysis in blood. It neutralizes both tissue-type PA and urinary-type plasminogen activator. PAI is present in endothelial cells, \( \alpha \)-granules of platelets and in plasma (Erickson, 1984; Sprengers, 1987). PAI determines the amount of free t-PA that is available for actual plasminogen activation and endogenous fibrinolysis. Thus, PAI plays an important inhibitory role in endogenous fibrinolysis. It is one of the most highly regulated fibrinolytic components. Changes in its activity may dramatically disrupt the normal fibrinolytic balance. Determination of PAI is hampered because the molecule is very unstable (Loskutoff, 1989). PAI antigen levels of normal human plasma may vary within the range 6.9 to 77 ng/ml. The same holds true for PAI activity levels which may vary from 1.9 to 12.4 U/ml (Nicoloso, 1988). The antigen assay may detect more PAI than the activity assay suggesting that some of the PAI in the sample is latent or in complex with t-PA. PAI activity in plasma frequently increases after surgery or in response to MI. This indicates that PAI is an acute-phase reactant.

PAI levels might be clinically important in MI, as is illustrated by at least 4 observations: a) Patients with coronary artery disease may have an impaired fibrinolytic activity (Chakrabarti, 1968), b) Reduced fibrinolytic activity was demonstrated in survivors of MI who had no coronary artery disease at angiography (Verheugt, 1987), c) Significantly elevated levels of PAI have been shown in survivors of MI compared to a healthy subjects (Hamsten, 1987), and d) Elevated PAI activity in the morning, in combination with almost undetectable free t-PA levels, corresponds with the documented higher incidence of MI during this part of the day (Muller, 1985; Tofler, 1987; Grimaudo, 1988; Angleton, 1989; Mulcahy, 1991). The inhibitory potential of PAI might easily be exceeded by infusion of rt-PA in patients with MI as was illustrated by an absence of correlation between the pre-existent PAI level and failure to achieve coronary patency with rt-PA (Sane, 1991). However, other authors showed an inverse relation of PAI levels before rt-PA or urokinase administration with vessel patency (Barbash, 1989; Sakamoto, 1992). Failure of rt-PA therapy in MI has also been explained by excessively high local concentrations of PAI caused by activated platelets in the coronary obstruction (Kruithof, 1986; Loskutoff, 1988). Thus, no consensus exists concerning the significance of plasma PAI levels in relation to the effect of thrombolytic therapy.

We did not find an increased PAI activity level in patients with a non-patent coronary vessel compared to those with a patent vessel following SK therapy (appendix 6). These results did not help to explain the superiority of a combination of non-fibrin and fibrin specific thrombolytic agents in patients with MI compared to monotherapy (Califf, 1991; Grines, 1991). These findings, however, were not confirmed by the GUSTO trial (GUSTO, 1993). Thus it may be concluded that the extent to which PAI may affect the success rate of thrombolysis in patients with MI still needs to be determined.

4. Impairment of plasminogen activation by lipoprotein(a) [Lp(a)]

In clinical practice, high levels of lipoprotein(a) [Lp(a)] have been associated with coronary artery disease, MI, coronary bypass vein graft stenosis, restenosis after percutaneous transluminal coronary angioplasty (PTCA) and cerebrovascular disease (Dahlen, 1986; Zenker, 1986; Hamsten, 1987; Hoefler, 1988; Hoff, 1988; Seed, 1990;
Hearn, 1992). Lp(a) was identified as an independent risk factor for atherothrombotic disease (Merz, 1989; MBewu, 1990; Loscalzo, 1990). Actually, its physiologic function is unknown but it is unlikely that the resemblance of apo(a) to plasminogen has no functional consequence in the fibrinolytic system (Brown, 1987; Scott, 1990; Rees, 1991). Clinical studies on Lp(a), however, are hampered because the various Lp(a) assays are poorly standardized. Dietary modification or drug therapy appeared to have little or no effect on Lp(a) levels (Brewer, 1990). In-vitro, Lp(a) appeared to enhance endothelial cell synthesis of PAI without altering t-PA activity. This suggested that Lp(a) might support a specific prothrombotic state (Etingin, 1990). In contrast, other investigators reported a more complex interaction (Edelberg, 1990).

In our study we found an inverse correlation between Lp(a) levels and plasminogen decrease, but only in patients with MI who had a non-patent coronary vessel at angiography after treatment with anistreplase (appendix 7). These results are in agreement with the hypothesis that high Lp(a) levels may impair fibrinolysis. It must be said that the number of patients in our study was small and the relation between Lp(a) and plasminogen decrease was only of borderline significance. Thus, definite conclusions may not be drawn. Because of the possible interaction between Lp(a) and PAI, it appears prudent to measure both parameters at the same time in further studies on factors which determine the outcome of thrombolytic therapy.

5. Proposed indicators of thrombolytic efficacy such as fibrinopeptide A (FPA)

Fibrinopeptide A (FPA) is liberated from fibrinogen when it converts to fibrin by the action of thrombin (Bettelheim, 1956; Mosesson, 1992). As a result, high FPA levels in plasma indicate thrombin activity and this reflects a status of hypercoagulability. The possibility of specific measurement by radio-immuno assay (RIA) made FPA a marker of fibrin generation in vivo. Elevated plasma levels have been demonstrated in patients with thromboembolic disease like MI but such levels decrease promptly in response to administration of heparin (Mombelli, 1984; Eisenberg, 1985). Treatment of MI with SK or rt-PA was associated with increased plasma FPA levels (Eisenberg, 1987; Rapold, 1989, 1990). No firm relation between perfusion status and plasma FPA levels has been reported following thrombolytic therapy. Whether thrombin/antithrombin III (TAT) complex levels may be used as an indicator for initial success of thrombolytic therapy was hypothesized (Gulba, 1991), but remains to be confirmed by other studies.

6. Conclusions and implications for thrombolytic therapy

When one considers coagulation parameters in relation to success of thrombolytic therapy with SK or anistreplase, only anti-streptokinase antibodies (aSKa) appear to affect its outcome in a direct manner. Former streptococcal infections and previous thrombolytic therapy with SK or anistreplase are responsible for elevated levels of aSKa. The antibody level was increased at the 3rd day after this treatment and levels remained elevated for up to 4.5 years (Blix, 1961; Massel, 1989; Jalihal, 1990; Lynch, 1991; Fears, 1992; Elliott, 1993; Lee, 1993; Patel, 1993; Buchalter, 1993).

The development of a simple and rapid enzyme-linked immunosorbent assay now
allows a more routine quantification of aSKa. These antibodies, which prevent the occurrence of a systemic lytic state, can also be identified indirectly by measurement of the fibrinogen level shortly after initiation of SK or anistreplase therapy. In case of a non-systemic lytic state, patency of the infarct related vessel was always absent. However, despite the occurrence of a systemic lytic state, success of thrombolytic therapy is not guaranteed. In these patients non-invasive parameters such as clinical condition, ECG ST-segment transformation and creatinine kinase levels, may offer clues with respect to infarct related vessel patency. These parameters, however, were not part of our studies. In our view, patients with high plasma levels of aSKa are candidates for additional or alternative treatment. This may include administration of a higher dosage of SK or administration of a different thrombolytic agent. Consequently, an improved reperfusion rate may ensue. Mechanical intervention in patients who fail to respond to pharmacological intervention is also optional but shall not be discussed here.

Besides efficacy, the presence of aSKa may also affect the safety of a repeated treatment with SK or anistreplase. Adverse events such as acute anaphylaxis, serum sickness, delayed hypersensitivity or vasculitis, which have been reported in 1.7 to 18% of SK or anistreplase recipients (Alexopoulos,1984; McGrath,1985; Bucknall,1988), are likely to occur more often following repeated treatment. Intra-dermal administration of a small dosage SK may be used for identification of patients at risk for adverse events mediated by IgE antibodies to SK (Dykewicz,1986). However, this test is not suitable for the assessment of IgG antibodies to SK. Only this type determines the efficacy of SK or its derivate. AST titers are frequently raised without corresponding elevated specific IgG titers (Elliott,1993). Thus, determining the plasma AST-level in the acute situation is not useful. For clinical practice it is important to ask patients for any previous thrombolytic treatment. Although comparative trials to guide the choice for repeated treatment have not been performed, both urokinase or rt-PA can be used safely and probably effectively in patients with reinfarction (White,1990b; White,1991).

Several authors have suggested that plasminogen activator inhibitor (PAI) levels might be relevant in MI. We studied its plasma level in patients with MI who received SK but found no association with the outcome of therapy. In contrast, for Lp(a) some evidence for impairment of clinical efficacy was demonstrated in non-patency. However, the relation between systemic levels of PAI and Lp(a) and the efficacy of thrombolytic therapy remains complex. This issue has to be studied further.