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Editorials

Platelet activation and coronary interventions

See pages 1207 and 1216 for the articles to which this Editorial refers

The importance of adequate anti-thrombotic therapy for the prevention of ischaemic complications of percutaneous transluminal coronary angioplasty (PTCA) was recognized early in the development of this technique. In the first description of coronary angioplasty in 1979, Andreas Grünzig and his colleagues treated their patients with a combination of heparin, aspirin and warfarin.[1] Their sagacious choice of aspirin as an anti-platelet agent has been supported in many subsequent randomized trials utilizing several other anti-thrombotic substances. The addition of agents such as dipyridamole, warfarin and dextran as well as prolonged high dose heparin treatment have not been shown to be of benefit in the management of these patients, and in fact may be detrimental in most routine instances.[2]

The question remains whether aspirin alone is sufficient to inhibit platelet involvement in acute thrombosis and late restenosis, or whether additional or different anti-platelet medications may result in a better clinical outcome.

Denudation of the normally thromboresistant endothelium and deeper arterial injury are inevitable for successful balloon angioplasty. At the site of arterial injury, platelets adhere to exposed collagen, von Willebrand factor and fibrinogen via integrin and non-integrin cell receptors. The attached platelets are then activated by several independent mediators which cause the release of chemotactic and thromboogenic factors as well as the induction of structural changes in platelet morphology. These changes result in the exposure of glycoprotein IIb/IIIa receptors that can bind fibrinogen provoking the generation of a platelet mass. These integrin receptors have been shown to represent the final common pathway for platelet aggregation. Through its inhibition of thromboxane A2 synthesis, aspirin can decrease platelet deposition and activation at the site of angioplasty. However, platelet aggregation induced by other mediators such as collagen, thrombin, adenosine diphosphate and serotonin is not affected.

In this issue, Kolarov et al.[3] report on the presence of activated platelets in a subset of patients undergoing coronary angioplasty despite treatment with high dose aspirin and heparin. They have previously reported that an increased circulating fraction of activated platelets is predictive for a poor short-term outcome after PTCA. They describe consumption of the activated platelet population in this subset of patients early in the procedure with a contrast medium-induced increase in the level of activated platelets in all patients. Two hours after PTCA they demonstrate a further increase in platelet activation. Their results support the view that with additional or superior anti-platelet therapy the outcome after coronary angioplasty may be improved.

The results of Kolarov et al. complement the findings of several other research groups. Gregorini et al.[4] have reported that addition of the second anti-platelet drug ticlopidine to standard aspirin therapy in PTCA decreased platelet activation as measured by CD62 and CD63 expression. Ticlopidine administration also inhibited the production of thrombin–anti-thrombin complexes as well as pro-thrombin fragment 1+2 (F1+2), reflecting a reduction of thrombin formation. These important effects of enhanced anti-platelet therapy on the coagulation cascade may further protect the patient from thrombus formation. In this regard, a preliminary study by Bertrand et al.[5] has shown beneficial effects of enhanced anti-platelet therapy with ticlopidine on ischaemic complications after PTCA, but no effect on the incidence of restenosis.

Similar to the results presented by Kolarov et al. in this issue, Neumann and his colleagues have identified the surface expression of the glycoprotein IIb/IIIa receptor, a marker of platelet activation, as a risk factor for subacute thrombosis after Palmaz-Schatz stent implantation.[6] A further report by the same group[6] has shown that treatment with ticlopidine at the time of stenting can inhibit post-procedural platelet activation.

Also appearing in this issue is a report examining aspects of the administration of the thrombin inhibitor recombinant hirudin (r-hirudin) by Hafner and co-workers.[7] They show the feasibility of administration of two doses of r-hirudin in patients with unstable angina undergoing coronary angioplasty with a dose-dependent correlation between the r-hirudin plasma levels and the partial thromboplastin time. As markers of coagulation, these investigators determined in the angioplasty}
the levels of thrombin–anti-thrombin complexes F1 + 2, and soluble fibrin (FM) in the heparin control and the r-hirudin treated patients. In these unstable patients only the higher dose (0.24 mg. kg⁻¹) of r-hirudin afforded effective periprocedural anticoagulation as determined by the markers of thrombin activity and conversion. Although clinical efficacy could not be assessed in this study, the inhibition of thrombin by r-hirudin has been shown in a large trial to result in a reduction in thrombotic coronary events early after PTCA⁸, which may be due to the effects of r-hirudin on thrombin-induced platelet activation.

A beneficial effect of anti-platelet therapy on both acute vessel closure and the process of restenosis was suggested by the results of the EPIC trial⁹. In this landmark study a chimeric monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor (c7E3), administered at the time of PTCA, was shown to reduce the incidence of acute ischaemic events by 35%. Clinical restenosis rates at 6 months were also reduced compared with those receiving standard care. The multicentre Helvetica trial⁸ showed a similar reduction in thrombotic coronary event rates with r-hirudin, however this did not translate into a long-term reduction in clinical events. This difference in long-term outcome may reflect the involvement of activated platelets in the restenosis process or may be a result of the action of c7E3 on other constituents of the damaged vessel wall. It is now recognized that the chimeric antibody c7E3 is not specific for IIb/IIIa receptors and will also bind to other integrins including vitronectin which is found on the luminal surface of endothelial cells and on the surface of smooth muscle cells. It is still not clear whether this lack of specificity is a desirable property. On one hand, binding of other integrins may improve the outcome of PTCA through induction of passivity in the vessel wall or through inhibition of smooth muscle cell proliferation and migration. Or, it may be that more specific and competitive inhibition of platelet IIb/IIIa receptors will result in an improved long-term outcome.

Other activated circulating blood components may be important in the process of restenosis. Pietersma et al.¹⁰ have shown the level of circulating activated monocytes prior to intervention, to be an independent predictor of late lumen loss after PTCA. Considered together, all of these findings may indicate a significant systemic component to acute closure and long-term restenosis following coronary interventions.

The results presented by Hafner et al. and Kolarov et al. are important for several reasons. Hafner et al. confirm that r-hirudin may be a suitable alternative to standard heparin therapy in patients with high risk unstable syndromes. Kolarov and his colleagues clearly demonstrate platelet activation at the time of angioplasty despite standard anti-thrombotic therapy and suggest that better anti-platelet therapy may result in an improved outcome. Conventional thinking assumes all patients who present for elective angioplasty are at low risk compared with those with acute coronary syndromes. Kolarov et al. show that this ‘low-risk’ population may be further stratified into low and higher risk by identification of those with significant platelet activation prior to any intervention. The activated platelets in these individuals are very quickly consumed at the time of the procedure. Since these patients have been shown to be at higher risk for ischaemic complication after angioplasty, it may be prudent to identify these patients early, before coronary intervention. Through early identification, this higher risk population may be targeted to receive more intense anti-platelet therapy, thereby protecting the population at lower risk from adverse side effects. Thus, with a more intelligent use of pharmacotherapy, both the short- and long-term success rate of PTCA may be significantly improved.

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References

Dual sensor pacing technology

See page 1251 for the article to which this Editorial refers

Sensors were first used in single-chamber pacemakers in the 1960s[1] but they did not become a serious implantable proposition until the 1980s[2,3]. Of these systems, one measures the time from the stimulus to the peak of the T wave: an interval which varies with the level of circulating catecholamines. In this way the pacemaker is able to determine the body’s metabolic demand and adjust its pacing rate to meet the perceived need. This was a brilliantly simple concept which proved to have problems in its application. Modifications were necessary throughout the 1980s to yield a fully effective device with one intrinsic drawback, that of a relatively slow physiological response at the onset of effort. It should not be surprising that a sensor depending on changes in catecholamine levels affecting the sensed time interval takes a finite time [>30 s] to respond.

In contrast, the other new device of the early 1980s is totally non-physiological as it senses vibration by means of a piezo crystal bonded inside the pacemaker’s can. Vibration begins immediately the wearer is active and so the response of the activity sensing device is instantaneous. However, vibration is not proportional to the degree of effort and certainly not a measure of the body’s metabolic need. The immediate response rises quickly over a short period and tends to level off during prolonged exercise of several minutes. It is at this point that the Stimulus-T sensing system carries an advantage because progressive and proportional changes in the measured interval occur during effort.

With much experience of these two sensors in separate devices as VVIR pacing systems, it seems logical to combine them in one pacemaker to attempt to obtain the benefits of both. The two sensing methods have the further advantage of not requiring a special pacing lead for their use. There is no situation in which the combination of a rapid response and a progressive response during sustained effort is more appropriate than in children. For this reason it is particularly interesting to read of the experience of the Turkish group reported in this issue[4].

There are potentially huge numbers of combinations of settings for these devices. The group investigated three basic sensor blendings and conclude that an equal balance or a leaning towards activity being dominant over Stimulus-T are the best in terms of chronotropic response to exercise both in the exercise laboratory and, more importantly, in daily life. Unfortunately, the group did not study the effects of, for example, an exciting television programme on heart rate which might have quite dramatically shown an advantage of the Stimulus-T system as high catecholamine levels combined with relatively little activity might be expected at such times.

There have been questions regarding the technological excess and high cost of devices such as these[5] which may be even more pertinent when dual sensors are combined with dual chamber pacing systems. However, it is only with clinical experience and good quality reports[6-7] that we can really appreciate the clinical value of more complex technology and increased expenditure.

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References