The battle of Vladimir

See page 1960 for the article to which this Editorial refers.

In 1966, the Russian director Andrej Tarkovski produced a feature film on the life of Andrej Roeblov, a 15th century monk and icon painter. Halfway through this 3 hour production, which is full of esoteric discussions on religion and art, the world comes suddenly to an end when the city of Vladimir, without any warning, is raided and destroyed by the Tartars. This event would subsequently have a decisive, profound influence on Roeblov’s remaining life and work[1].

In general, we prefer to perceive history as a logical continuum with a certain purpose, rather than a random process in which progress is the result of sudden and unexpected changes in tradition or habit. For instance, it is questionable whether Andreas Grünntzig seriously contemplated the abolishment of coronary artery bypass surgery (CABG) as a treatment of coronary artery disease when he introduced percutaneous transluminal coronary angioplasty (PTCA) in 1977[2]. Nevertheless, what started 22 years ago as an experiment by a single individual, gave rise to an entire change in culture: PTCA became an acceptable alternative to CABG. Indeed, the indication was initially limited to single vessel disease in patients with stable coronary artery disease. However, this changed as a result of yet another creative idea. Richard Schatz added 1·0 mm of stainless steel to the slotted tubular design Palmaz stent[3]. This small, centrally located articulation provided the stent with flexibility, thus making it more suitable for intra-coronary implantation. Again, it is unlikely that Julio Palmaz and Richard Schatz foresaw that, in addition to dealing with the problem of PCTA-related acute occlusion, stents could reduce balloon angioplasty related restenosis rates. However, the truth is stents did[4,5]. And subsequently, the ‘stent frenzy’ that marked the end of the previous century, gave rise to the current situation in which stent implantation has become the default therapy for patients with single and multivessel coronary artery disease alike[6]. In addition, the effectiveness of PTCA with stents as a treatment of unstable coronary syndromes, including acute myocardial infarction, has been demonstrated in an increasing number of studies[7,8]. The introduction of abciximab, a potent antiplatelet drug, as an adjunct to stent implantation has been of specific importance within this context[9]. Even the ‘long-standing taboo’ of left main disease has successfully been re-addressed in a recent study by Park et al[10]. Consequently, in a world where on a yearly basis more patients are treated with PTCA than with CABG, the question emerges whether CABG ‘is here to stay’[11].

If it is not acute myocardial infarction, multivessel disease, or left main disease, then the question is what is the true remaining, primary indication for CABG? The initial reports in the literature on results of PTCA for chronic coronary occlusion indicated that the procedural success rates were low[13]. In addition, as compared to long-term results of PTCA for dilatation of coronary stenoses, successful PTCA for chronic occlusion seemed to be plagued by a significantly higher incidence of restenosis and reocclusion. Nevertheless, it became apparent that long-term maintenance of blood flow through a previously occluded coronary artery had a positive influence both on left ventricular function and clinical outcome[13,14]. Various new guidewire technologies have been developed in an attempt to increase procedural success rates[15], while, also in this setting, intracoronary stents have proven their value[16–18]. Following previous and comparable studies, such as the SICCO (Sirmes et al.), the TOSCA (Buller et al.) and the SPACTO Trial (Höher et al.), the Israeli Working Group for Interventional Cardiology performed the STOP Trial (Stents in Total Occlusion for restenosis Prevention). In this issue Lotan et al. describe the results of the STOP Trial in which patients were randomized to either balloon angioplasty or balloon angioplasty plus stent implantation following successful recanalization of chronic coronary occlusions[19].

In agreement with the aforementioned studies, stent implantation in the STOP Trial resulted in a significant reduction of the angiographic binary restenosis rate (70·9% in the PTCA arm vs 42·1% in the stent arm). Likewise, stenting resulted in a 51% relative reduction of the reoclusion rate (respectively 7·9% vs 16·1%). Of interest was an unexpected, additional finding. Restenosis in the PTCA study-arm had a predominantly focal aspect, occurring within 5 mm of the site of the original occlusion. In contrast, in the stent study arm, in-stent restenosis had a more diffuse character. As diffuse in-stent restenosis is a particularly therapy for resistant disease, the importance of this finding is centred on the advice by the authors to use stents following successful recanalization, but to restrict stenting to the use of short stents at the site of the original occlusion. Unfortunately, the STOP Trial was under-powered to draw definitive conclusions.
about this restenosis pattern. However, if this preliminary finding could be confirmed in a subsequent study the results would have a major impact on the approach to percutaneous reconstruction of occluded coronary arteries.

Although the outcome of various ‘stent versus balloon angioplasty’ trials are encouraging, some aspects remain troublesome. The randomization in the SICCO, TOSCA, SPACTO and STOP Trials was performed after successful passage of a guidewire through the occlusion. Therefore, the success rate of guidewire crossing in the entire study cohort (that is: prior to randomization) was not relevant for the study outcome. In the SPACTO Trial, the only randomized stent vs balloon study to report this information, the success of recanalization was no more than 62%. In the TOTAL Trial, which focused on guidewire success in chronic coronary occlusion by using the laser guidewire, the crossing success was even lower, as it did not exceed 53%. Therefore, it seems that although mechanical hardware available for coronary angioplasty continues to be refined, restoration of blood flow through a chronically occluded coronary artery still remains a true challenge. The second reason for concern is that although stents reduce restenosis rates, the recurrence rates after stenting for chronic occlusion significantly lag behind those achieved in stent trials for non-occlusive disease. In the above mentioned studies the stent restenosis rates ranged from 32% to 55%. Therefore, rather than rejoice on the success of stenting for chronic occlusion, we should emphasize that the problems of how to open a chronic occlusion and subsequently guarantee long-term vessel patency are far from being resolved.

What could we do to make things better? Sometimes the answer to a problem comes from looking at the problem from a different angle. Optical coherence reflectometry is a new high resolution intravascular imaging technique, which can be used to distinguish atherosclerotic plaque from normal vessel wall. Incorporated in a guidewire, this technique could prove to be useful in facilitating angioplasty of occlusions refractory for recanalization with conventional guidewires. The initial results with this system were recently presented\(^{[20]}\). More sophisticated new, non-invasive three-dimensional imaging modalities such as magnetic resonance imaging or electron beam computed tomography might prove useful for (pre-procedural) evaluation of the anatomy of the ‘missing’ coronary segment. Whether these techniques will evolve into on-line 3D guidance systems for intra-coronary interventions remains to be seen.

Intracoronary brachytherapy with gamma irradiation has been shown to be potentially beneficial in the treatment of in-stent restenosis in a small patient cohort\(^{[23]}\). Whether brachytherapy with gamma- and/or beta irradiation should be applied in total occlusions, in order to improve vessel patency rates remains to be seen. The possibility that brachytherapy as and adjunct to coronary athrectomy could contribute to further preserving of optimal acute results certainly merits additional study.

In conclusion, despite many years of technical development, PTCA is not yet fully competitive with bypass surgery for the treatment of chronic coronary occlusion. However, with novel imaging, guidance and therapeutic modalities ‘around the corner’ the issue is maybe not ‘if’ but ‘when’ we will beat the Tartars in the battle for Vladimir.

J. N. HAMBURGER
P. W. SERRUYS
University Hospital Rotterdam Dijkzigt, Rotterdam, The Netherlands

References


Reperfusion synergism: will it be both sustained and safe?

See page 1944 for the article to which this Editorial refers

‘Would ye both eat your cake and have your cake?’
John Heywood

The past 15 years have witnessed remarkable advances in the pharmacological approach to reperfusion therapy for acute ST segment elevation myocardial infarction. The GISSI investigators established the life-saving potential of intravenous streptokinase[1]. The ISIS-2 investigators not only reaffirmed this but identified the important and separate role of aspirin and then, using a 2 x 2 factorial design, demonstrated a powerful interaction between the modest platelet inhibitory effects of aspirin and a non-fibrin-specific fibrinolytic agent[2]. Enhanced understanding of the biochemical mechanisms underlying the balance between endogenous clot formation and dissolution, coupled with recombinant technology, modulated the next major breakthrough, i.e. the development of tissue plasminogen activator as a fibrin-specific, potent, short-acting therapy[3]. Optimal deployment of this agent requires concomitant antiplatelet therapy and thus it became conventional to incorporate intravenous heparin and aspirin with rt-PA in a tripartite approach[4].

Paradoxically the endogenous forces promoting coronary thrombosis are accentuated by fibrinolytic therapy alone, which accentuates platelet aggregation and exposes fresh thrombin at the clot surface: this in turn amplifies the conversion of fibrinogen to fibrin and also stimulates platelet aggregation[5].

Because recent research demonstrates that platelets comprise a major portion of the coronary thrombus, it has been surmised that failure to break through the ‘thrombolytic ceiling’ may in large part be attributable to the inability of conventional fibrinolytics to overcome this impediment[6]. Further fuel for this argument is derived from the insightful studies of Ito and colleagues who demonstrated a discordance between TIMI 3 coronary patency and microvascular flow in the distribution of the culprit vessel[7]. This finding in 23% of 39 cases with anterior myocardial infarction is likely attributable to microemboli from platelets and other sources as well as vascular endothelial dysfunction comprising the ‘no reflow syndrome’.

Concomitant with these observations has been the emergence of intravenous glycoprotein IIb/IIIa inhibitors directed towards the final common pathway of platelet aggregation[8]. Unlike fibrinolytic therapy, they have been clearly shown to enhance outcomes in patients with non-ST elevation myocardial infarction and unstable angina[9]. They also permit safer and more effective mechanical coronary intervention and their use has been extended to partnering with primary angioplasty as therapy for acute ST segment elevation myocardial infarction. Indeed the use of abciximab alone, the initial agent developed in this class, demonstrates the capacity to ‘disaggregate’ recent coronary thrombus in myocardial infarction with restoration of coronary...