INTERVENTIONAL PROCEDURES FOR ATHEROTHROMBOSIS: PATHOLOGY OF RETRIEVED MATERIAL

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The clinical approach to atherosclerotic disease has dramatically changed, thanks to the recent improvements in interventional revascularisation procedures.^{w1} The mechanical relief of arterial obstruction through the introduction of a catheter into the arterial system to alleviate symptoms and reduce ischaemia and to prevent necrosis has been applied to all the important arterial networks: carotid, coronary and peripheral arteries. Removing the plaque and thrombus through an endovascular catheter without a surgical operation has offered a unique opportunity to obtain and study the retrieved material and to make clinicopathological correlations, thus allowing a better understanding of the atherothrombotic phenomenon. The target of non-surgical percutaneous interventional procedures is to debulk obstructed arteries. This result can be achieved through different approaches and mechanisms.

CATHETER-BASED PROCEDURES

Catheter-based procedures for revascularisation can be divided into two different groups according to the main mechanism responsible for restoration of blood flow.

- ▶ The first group encompasses angioplasty and stenting, in which the mechanism involves stretching, fragmentation and squeezing of the plaques and thrombus; the plaque is crushed outwards against the arterial wall, while the arc of the circle by the arterial wall spared by the plaque lesions is over-stretched.
- ▶ The second group encompasses directional, rotational and transluminal extraction catheter atherectomy, in which the mechanism of debulking is either cutting with retrieval or aspiration, or pulverisation/grinding followed by removal with embolisation of the material. With directional atherectomy the catheter tip is equipped with a bladed device that cuts away the plaque and stores the fragments collected by multiple cuts in a tiny container. Soft and non-calcified material is usually obtained with the application of such devices; during rotational atherectomy a rot ablator tip is guided to pulverise mainly calcified plaque and the ground up micro particles can travel through the circulatory system. With transluminal extraction atherectomy the catheter is equipped with a rotating blade and a hollow tube to cut away and suck the plaque into the tube, and it is mainly applied to obstructing lesions containing blood clots.

Because of the higher rate of restenosis, atherectomy is nowadays performed less frequently than balloon angioplasty and stenting, being confined to difficult to treat lesions such as calcified lesions.

INTERVENTIONAL PROCEDURE AND PLAQUE DESTABILISATION

Our understanding of the atherosclerotic process is derived from the definition of the two different types of lesions, the stable and the vulnerable plaques, and from the understanding of the mechanisms that lead to the conversion of a stable into an unstable, rupture-prone vulnerable plaque.^{1–3 w2} Acute clinical events are determined by the fragile structure and composition of the atherosclerotic lesions rather than the degree of stenosis itself. A vulnerable lesion is characterised by: a highly thrombogenic lipid-rich core, occupying more than 40% of the lesion, the type of lipid (cholesteryl ester softens the plaque), and consistency and temperature of the lipid core; a thin cap overlying the atheromatous core, consisting of a dynamic structure with extracellular matrix synthesis and degradation modulated by many factors, among them inflammation, apoptosis and metalloproteases; inflammatory cell infiltrate, confined to the fibrous cap, and often to the edge of the plaque, which modulates the remodelling process and which can favour the rupture of the thinner cap or erosion of the endothelium. A stable lesion is regarded as being composed of smooth muscle cells, extracellular matrix glue, few inflammatory cells, a thick cap, and no or little extracellular lipid.

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Figure 1 Effects of interventional vascular procedures on plaque lesions, leading to “embolising plaque”. Mechanical debulking produces a dislocation of small atherothrombotic fragments which are able to move distally into the circulation.

Interventional procedures always result in modification of the atherosclerotic lesion, however stable or unstable it may be, to that of an embolising plaque^{4 w3} (fig 1). This gives rise to unstable lesions and therefore modifies the natural history of the plaque itself. Mechanical debulking, through pulverisation, fragmentation, squeezing and cutting, produces a dislocation of

small atherothrombotic fragments which are able to move down distally into the circulation. These particulates can be entrapped in the microvasculature, becoming vasoactive and, according to some authors, also causing the no-reflow phenomenon (fig 2).

CONSEQUENCES OF PLAQUE DESTABILISATION

The consequences of plaque remodelling may imply remote “propagation of arterial thrombi”. This embraces a very complex pathophysiological cascade involving local and remote phenomena. This article will not address the local phenomena, but it must be mentioned that this local injury produces an early activation of propagating factors for thrombus growth and exposure of subendothelial matrix, with the subsequent development of the more complex process of plaque remodelling.

The remote propagation is, in other words, the microembolisation of disrupted plaque (fig 1). We do not have to envisage microembolisation as a simple mechanical phenomenon, because it is accompanied by a release of bioactive materials, endothelial and platelet mediators and inflammatory or pro-inflammatory substances. Plaque disruption causes release of fragments which are trapped in the microvasculature causing mechanical blockage. It is obvious that the major factor determining mechanical blockage and its consequence, which is the degree and extension of ischaemia, is the interplay between particle size and vasculature dimension. The larger the size of the particles, the earlier they get trapped resulting in more clinically significant ischaemia. But if particle size does not change, microvasculature diameter can, because it is

Figure 2 Pathophysiology of microembolisation phenomena, including the two components of mechanical and functional obstruction. Plaque disruption causes release of fragments which are trapped in the microvasculature, causing mechanical blockage. The released mediators cause vasospasm, and endothelial dysfunction with a functional superimposed obstruction. The result of both mechanical and functional blockage is the no-reflow or impaired flow phenomenon.

responding with vasoconstriction to the released mediators. Moreover, once the microvasculature is blocked thrombosis can occur and extend backwards. This process is enhanced by the presence of thromboxane 2, tissue factor originating from inflammatory cells and fibrin.

We will try to provide a comprehensive view of these events to depict possible clinical scenarios which may arise. There may be substantial variations, both pathophysiologically and clinically, in the different vascular areas. The cerebral arteries differ from the coronaries in terms of vessel dimension, collateral circulation, nature and composition of the plaque, and susceptibility of the endothelium to local and circulating vasoactive, thrombogenic inflammatory substances. The clinical consequences and symptoms related to ischaemia are entirely dependent on these differences. For these reasons we will discuss the cerebral and coronary procedures separately, but will nonetheless try to draw some conclusions, allowing a comparison between them.

LESSON LEARNED BY THE STUDY OF ATHERECTOMY MATERIAL

The ability to obtain materials from interventional vascular procedures has allowed investigators to develop a greater understanding of the natural history of the atherosclerotic plaque and the development of acute coronary syndromes.

Role of apoptosis in atherosclerosis

In atherosclerosis, cell accumulation and proliferation along with cell death contribute to lesion progression and plaque evolution.^{5 w4} Loss of cells in atherosclerosis is attributed to both necrosis and apoptosis. The loss of smooth muscle cells (SMCs) which produce the extracellular matrix (ECM), the main component of the fibrous caps, coupled with the degradation of the ECM by macrophage metalloproteinase, weakens the fibrous caps and increases the likelihood of plaque rupture and acute events. This is supported by the presence of fewer SMCs, reduced collagen and glycosaminoglycans, and more macrophages in the ruptured plaques. Apoptotic cell death is an important pathogenetic event in atherogenesis. SMC apoptosis has been observed both in normal arteries, in atherosclerotic lesions, and in SMC cultures derived from these normal and affected arteries. A higher apoptotic index has been shown in advanced (types V and VI) than in early lesions (types I–III). Also, based on studies using an experimental animal model of balloon angioplasty, apoptosis could be viewed as the main cause of early SMC loss after balloon injury in the media of the vessels and could be still present 72 h after the angioplasty. Later on when the signalling for growth stops, minimal levels of apoptosis are still detectable, suggesting that this mechanism also modulates the cellularity of the lesions.⁶

Unstable versus stable plaques

Rupture of coronary plaques containing a lipid rich core, with subsequent thrombus formation, has been implicated as the central mechanism responsible for transformation of stable or asymptomatic coronary lesions into unstable plaques causing acute coronary syndromes. It is now well recognised that inflammatory processes play an important role in plaque rupture. Unstable “vulnerable” plaques have thin fibrous caps with reduced collagen content, fewer vascular smooth muscle

cells (VSMCs) and large lipid cores with an increased number of activated inflammatory cells.

Nuclear factor- κ B (NF- κ B), a transcription factor which plays a coordinating role in inflammation and cellular proliferation, is thought to be involved in the pathogenesis of atherosclerosis and plaque destabilisation.

Certain stimuli, including cytokines and oxidants such as oxidised low density lipoprotein, lead to the activation of NF- κ B. This results in the translocation of NF- κ B into the nucleus and subsequent binding to the promoter regions of target genes.

Coronary atherectomy plaque specimens, obtained via directional coronary atherectomy from patients with unstable angina pectoris (UAP) and stable angina pectoris (SAP), have shown that activated NF- κ B is significantly higher in UAP compared with SAP, supporting a role for NF- κ B in the pathogenesis of acute coronary syndromes.^{7 8}

Native versus restenotic plaque

In-stent restenosis (ISR) is a major complication following stent implantation. Several studies have reported on the intralésional changes after stent implantation, underscoring migration and proliferation of SMCs. However, it is unclear whether these cells derive from the arterial wall, from extravascular sources or from circulatory precursor cells. Several lines of evidence have recently revealed the presence of pluripotent mesenchymal cells originating from primarily extravascular reservoirs such as the bone marrow. Likewise, a few reports showed rapid, transient mobilisation of endothelial precursor cells after vascular trauma and the presence of bone marrow derived cells in solid neointima or in lesions after allografting.^{9 w5}

A major finding of human ISR in coronary and peripheral vessels is its hypercellularity, which differs notably from de novo lesions and is consistent with previous work demonstrating hypercellularity. Traditionally, intimal hypercellularity and the development of ISR have been attributed to migration, proliferation and mitigated apoptosis of SMCs.

Signals for bone marrow derived endothelial progenitor cells and dendritic cells, as well as neural crest derived cells, were found in all atherectomy probes with ISR origin; specific staining was increased 2–9-fold in ISR tissue compared to de novo plaques, suggesting the recruitment of primarily extravascular cells to contribute to neointima formation after stenting. The predominant proportion of neointimal cells (67%) bear the marker α -SM actin, whereas up to 10% of the residual cells reveal distinct signals for bone marrow or neural crest derived cells.

LESSON LEARNED BY THE STUDY OF PROTECTION DEVICES

Percutaneous transluminal intervention for atherosclerosis has become well established for coronary arteries, peripheral arteries and carotid vessels. However, its major drawback is represented by a high incidence of periprocedural and procedural complications as a result of distal embolisation of thromboembolic material. New evidence has underscored the frequency and prognostic importance of embolisation in the distal microvasculature and has fostered the introduction of devices for protecting the distal arterial tree from embolisation during both elective or emergency procedures.⁴ Different types of devices have been developed: filter devices, comprising

Different systems of cerebral protection to reduce distal embolisation

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Figure 3 Different systems of cerebral and coronary artery protection developed to reduce distal embolisation: balloon distal occlusive devices, filter devices using different baskets, and proximal balloon occlusive devices.

baskets able to capture tissue fragments, distal and proximal balloon occlusive devices (fig 3), and aspiration systems. From the use of protection devices we have gained a substantial knowledge in regard to clinical outcomes after protection, and an understanding of the pathophysiology of the local and remote consequences of plaque destabilisation by means of the study of retrieved material.

Carotid artery procedures

Stent placement for extracranial carotid artery disease has emerged as a potential alternative to carotid endarterectomy, which is still the current gold standard treatment for carotid artery stenosis. However, compared to the surgical approach, percutaneous carotid stenting is accomplished with an increased incidence of microemboli as shown by transcranial Doppler monitoring. These emboli are associated with a higher neurological complication rate and are also recognised as a potential cause of periprocedural stroke during endarterectomy.^{10 w6}

Few studies have given detailed morphologic evaluation of the material retrieved during percutaneous intravascular procedures.^{11 12 w7 w8} From these studies it appears that most of the embolic dissemination occurs during iatrogenic manipulation of the atheromatous plaque.

Protection devices have the potential to reduce the incidence of intracranial debris embolisation and render percutaneous carotid artery revascularisation safer.^{13 w9 w10}

In our own experience, histopathological analysis has resulted in a better understanding of the quantity, particle size, and composition of embolised debris collected in protection filters during carotid artery stent implantation of the internal carotid artery with >70% diameter stenosis (mean (SD) 82.1 (11.1)%). The study revealed the presence of debris in a high percentage (up to 80%) of the cases, with more than half of the polyurethane membrane filter covered with material composed of fibrin strand-entrapped platelets, leucocytes and red cells suggestive of thrombus material, fibrous tissue, calcium spots, soft acellular and amorphous material, macrophages, foam cells and more rarely cholesterol clefts, typically

identifiable in atheromatous plaques^{w8} (fig 4). Most importantly, the embolic burden was made up of a cluster of particles of different sizes, ranging from 1.08–5043.5 μm (mean 289.5 (512) μm) in the major axis and 0.7–1175.3 μm (mean 119.7 (186.7) μm) in the minor axis. Particles >300 μm were found in all filters with debris and 52% of filters presented particles >1000 μm . This is the clinical confirmation of the experience with filter protection in the ex-vivo model reported by Ohki *et al.*¹¹

The same results were obtained with different protection devices such as the occlusive balloons, with debris retrieved in 81%^{w11} to 100%^{w12} of the performed procedures. It is important to note that the microcirculation encompasses vessels with a diameter of <300 μm . The dimensions of the arterial network ranges from the aorta to arteries up to 400–300 μm , small arteries with diameters between 300–100 μm , arterioles with diameters between 100–12 μm , and capillaries with diameters of around 12 μm . A problem is whether some of the retrieved thrombotic material could have been locally produced inside the filter, but this is still an open question. It is assumed that not all captured particles would have produced acute clinical sequelae. The significance of clinically silent embolisation during carotid artery interventions has not yet been established and possibly microvascular obstructions are difficult to be recognised. However, according to recent observations,^{w13} emboli can potentially trigger platelet aggregation and may amplify microvascular obstructions.

Since cerebral protection is a safe procedure and it limits intracranial debris embolisation, the use of protection devices during percutaneous carotid artery stenting is strongly supported. Roubin *et al.*¹⁴ have reported the important reduction of the periprocedural complication rate over 5 years of experience from 9.3% in the first year to 4.3% in the fifth year. This was probably due to refinement of stenting techniques and newly developed equipment. In order to achieve the target of $\leq 3\%$ periprocedural complication rate recommended by the American Heart Association/Society of Vascular Surgery guidelines for the treatment of asymptomatic patients, cerebral protection may well become essential. Data from multiple registries and trials have demonstrated that carotid artery angioplasty and stent placement is an effective means of treating carotid artery stenosis; it has come to be considered as first line therapy in the management of carotid artery stenotic disease in individuals at high risk for complications related to surgical intervention.^{15 w14}

Coronary artery procedures

The microembolisation phenomenon during procedures of stent implantation in native coronary arteries of patients with different acute coronary syndromes (stable and unstable angina) has shown the different characteristics of the debris captured by the filter and has revealed the relation between clinical and angiographic variables and pathological data.¹⁶ Embolisation of a significant amount of plaque fragments is a common event after stent implantation in native coronary arteries of patients with both stable and unstable angina. Particles can be detected in up to 75% of the filters, with a mean particle size of 582 (320) μm . Moreover, particles >300 μm and fragments >1000 μm can be seen in a considerable number of cases. Analysis of particle size distribution reveals

Debris embolised during carotid artery stenting with filter protection

Figure 4 Debris embolised during carotid artery stenting with filter protection. (A) Inside of the polyurethane plastic filter membrane after removal of the metallic wire containing embolised fragments. (B–D) Histology of some retrieved particles. (B) Note the necrotic material, cholesterol clefts, and thrombus. Haematoxylin and eosin staining. Original magnification $\times 6$. (C) Note the thrombus with fibrin and blood cells. Haematoxylin and eosin staining. Original magnification $\times 31$. (D) Detail of fibrin-platelet thrombus and fibrocellular fragments. Masson trichrome stain. Original magnification $\times 80$.

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that more than 60% of the fragments have the potential for obstructing small arteries even before they reach the microcirculation.

The magnitude of embolisation, assessed in terms of size and the number of particles, does not correlate with plaque size measured angiographically, suggesting that plaque composition

is more important in determining embolisation. Unstable lesions and lesions from older patients release larger embolic particles. This finding is consistent with the observation that coronary stenting in unstable angina is associated with a greater incidence and magnitude of myocardial injury. Eccentric lesions produce larger emboli, a finding which is in

Filter protection during coronary artery stenting

Figure 5 Filter protection device retrieved after coronary artery stenting showing the retrieved particulates (A) in the filter device. (B) Inside of the polyurethane plastic filter membrane after removal of the metallic wire containing embolised fragments. (C, D) Histology of retrieved particles (haematoxylin and eosin staining). (C) Note the thrombus with fibrin and blood cells and calcium precipitates. Original magnification $\times 10$. (D) Detail of fibrin-platelet thrombus and fibrocellular fragments. Original magnification $\times 62$.

keeping with angiographic studies demonstrating that eccentric and complex stenoses are markers of histologically “complicated” and more unstable plaque.^{w15}

There are several studies demonstrating that distal protection, using either occlusion balloons or filtering devices, are effective in preventing embolisation of atheromatous material dislodged by mechanical plaque disruption during vascular interventions. This is true both for native coronary arteries^{13 17 w8 w16 w17} but also for saphenous vein grafts.^{w18 w19} Until the advent of embolic protection devices, saphenous vein graft intervention suffered from high rates of no-reflow (up to 8% of the procedures) and post-procedural myocardial infarction (17–30% of procedures) secondary to atheroembolic debris. Occlusive and filter embolic protection have become the standard of care in the management of these patients, reducing major adverse cardiac event (MACE) rates by 40–50%. The safe trials, comparing protected and non-protected patients, showed a statistically significant drop of the no-reflow phenomenon as well as a reduction in MACE and non-Q wave myocardial infarction.^{w19}

From a clinical point of view, distal microembolisation of the coronary circulation is the most frequent cause of periprocedural increases of biochemical markers of myocardial necrosis, even in otherwise successful procedures, and this is associated with an unfavourable long term outcome.⁴ The role of embolising debris in causing microvascular obstruction during coronary interventions is clearly shown by several studies. Indeed, the size of most of the emboli trapped by the filter is far too large to cross the microvascular bed. Another in vivo demonstration of the role of microembolisation in determining thrombus propagation is provided in the study by Kotani *et al*,¹³ who showed that, in patients with acute coronary syndromes undergoing percutaneous interventions, larger amounts of plaque debris can be aspirated from the target vessel when no-reflow occurred. Although glycoprotein IIb/IIIa inhibitors have been shown to reduce the incidence of periprocedural myocardial infarction, pharmacological treatment cannot be expected to play a major role when large amounts of plaque, especially non-thrombotic material, are embolised distally.

Embolised particles are characterised by fibrin strand, entrapped platelets, leucocytes and red blood cells suggestive of thrombus material, fibrous tissue, calcium spots, soft acellular and amorphous material, macrophages, foam cells, and more rarely cholesterol clefts, typically identifiable in

Figure 6 Scatter plot demonstrating the particle size and number of fragments captured during carotid, coronary and saphenous vein graft (SVG) stenting.

Percutaneous vascular interventions for the relief of atherothrombosis: key points

- ▶ Microembolisation is the rule during percutaneous vascular intervention procedures such as angioplasty or stenting
- ▶ Debris collected with protection devices are composed mainly of foam cells, cholesterol clefts, amorphous material, fibrous tissue fragments and platelets, erythrocytes, leucocytes and fibrin, derived by squeezing and fracturing of the atheroma and thrombus during the procedures. Other vasoactive substances can be released as well
- ▶ A higher embolisation burden is due to plaque composition, and native and unstable lesions
- ▶ No-reflow phenomenon is the result of mechanical and functional microvascular obstruction
- ▶ Particles can vary in size but frequently are larger than 300 µm
- ▶ Thrombus material can be of different ages, from fresh to organised (even a few weeks old), suggesting that thrombus formation can precede symptom onset and occlusive events

atheromatous plaques (fig 5). The thrombotic components, however, exceed the non-thrombotic ones by a ratio of 3:1.

In acute myocardial infarction with and without ST segment elevation, a recent randomised trial, evaluating whether distal protection with a filter device can improve microvascular perfusion and reduce infarct size after percutaneous catheter intervention, failed to reveal improvement in reperfusion or reduction in myocardial injury to a perceptible extent. However, a subgroup of patients, presenting within 6 h from the onset of pain, derived a significant benefit (in terms of MACE) from the use of a filter wire.^{18–20} This leads us to another important lesson derived from the study of these retrieved materials: there is a discrepancy between the age of the thrombus and the symptom onset of acute coronary syndromes. The unstable plaque producing an acute coronary syndrome has a natural history in terms of complications which goes back days if not weeks before the onset of symptoms. The paper by Rittersma *et al*¹⁹ clearly demonstrates that intracoronary thrombi, aspirated during angioplasty in patients with acute ST elevation myocardial infarction, were days or weeks old, indicating that sudden coronary occlusion is often preceded by a variable period of plaque instability and thrombus formation initiated days or weeks before onset of symptoms.

Our experience with an aspiration catheter before stenting during percutaneous coronary intervention (PCI) in acute myocardial infarction confirmed the safety and feasibility of this procedure. Using this device during PCI in a patient with acute myocardial infarction limits distal embolisation and avoids predilatation before stenting. After thromboaspiration, the TIMI (Thrombolysis in Myocardial Infarction) score was ≥ 2 in 79.2% patients. The procedure was successful in 98% of patients (TIMI ≥ 2 and residual stenosis $< 30\%$) and in hospital MACE were observed in 5% of the procedures. It is interesting to note that procedures on the right coronary artery gave rise to a larger amount of debris compared to the anterior descending and circumflex coronary arteries and that no correlation was found with the use of glycoprotein IIb/IIIa inhibitors and chest pain–PCI time. Taking into account that debris was present in 86% of cases, and that it comprised mainly thrombotic material,

foam cells and cholesterol clefts, we can safely argue that avoidance of microembolisation provides a further improvement in the treatment and outcome of acute coronary syndromes.

CONCLUSIONS

Interventional procedures produce plaque destabilisation with thrombus propagation, subsequent microembolisation and consequently ischaemia which can even result, in the worse case scenario, in the no-reflow phenomenon. This is common to all the vascular regions although the coronary circulation is profoundly different from the cerebral circulation. Even the atherosclerotic lesions of the coronary tree are different from those of the extracranial carotid arteries. Our experience with retrieved material shows debris collected from carotid arteries has an average size twice that of material collected from coronary arteries (fig 6). This of course depends on the sizes of the artery, lesion and balloon, and differences related to the procedure itself. What it is striking, however, is the size of the largest collected particles which is up to 2500 µm for the coronaries and 5000 µm for the carotid arteries. Although a comparison cannot be made, certainly these emboli can block arteries of 2500–5000 µm. The scenario is worse for coronary arteries where the relationship of vessel size to embolus size is less favourable. It is interesting to note that symptomatic patients have larger collected debris than asymptomatic ones, as is the case for patients with acute coronary syndrome compared to those with stable angina. This is another demonstration that unstable lesions are more likely to embolise once a procedure is performed, thus providing the rationale for using protection devices during interventions. We must investigate how the advantages of these procedures can be applied to the different clinical settings and patient subgroups; for the moment, however, they represent one of the most efficacious tools we possess for avoiding ischaemia and no-reflow caused by microembolisation, especially in high risk patients with acute coronary syndromes and symptomatic carotid artery patients.

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REFERENCES

- 1 Naghavi M, Libby P, Falk E, *et al*. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. *Circulation* 2003;**108**:1664–72.
- 2 Naghavi M, Libby P, Falk E, *et al*. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. *Circulation* 2003;**108**:1772–8.
- 3 Spagnoli LG, Mauriello A, Sangiorgi G, *et al*. Extracranial thrombotically active carotid plaque as a risk factor for ischemic stroke. *JAMA* 2004;**292**:1845–52.
- ▶ Ruptured plaques of patients affected by stroke were characterised by the presence of a more severe inflammatory infiltrate, comprising monocytes, macrophages and T lymphocyte cells, compared with that observed in the transient ischaemic attack and asymptomatic groups, demonstrating a major role for carotid thrombosis and inflammation in ischaemic stroke in patients affected by carotid atherosclerotic disease.
- 4 Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;**101**:570–80.
- ▶ This review highlighted the role of the microembolisation phenomenon, with distal dislocation in the tributary circulation of vasoactive substances and tissue and thrombotic fragments in atherosclerotic vascular disease.
- 5 Schoenhagen P, Vince DG, Ziada K, *et al*. Relation of matrix-metalloproteinase 3 found in coronary lesion samples retrieved by directional coronary atherectomy to intravascular ultrasound observations on coronary remodelling. *Am J Cardiol* 2002;**89**:1354–9.
- 6 Angelini A, Visonà A, Calabrese F, *et al*. Time course of apoptosis and proliferation in an animal model of balloon vascular injury. *Basic Appl Myol* 2002;**12**:33–42.
- 7 Hatakeyama K, Hao H, Imamura T, *et al*. Relation of CD39 to plaque instability and thrombus formation in directional atherectomy specimens from patients with stable and unstable angina pectoris. *Am J Cardiol* 2005;**95**:632–5.
- 8 Wilson S, Best P, Edwards WD, *et al*. Nuclear factor-κB immunoreactivity is present in human coronary plaque and enhanced in patients with unstable angina pectoris. *Atherosclerosis* 2002;**160**:147–53.
- 9 Skowasch D, Jabs A, Andrie R, *et al*. Presence of bone-marrow and neural-crest-derived cells in intimal hyperplasia at the time of clinical in-stent restenosis. *Cardiovasc Res* 2003;**60**:684–91.
- 10 Ackerstaff RG, Moons KG, van de Vlasakker CJ, *et al*. Association of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke* 2000;**31**:1817–23.
- 11 Ohki T, Roubin GS, Veith FJ, *et al*. Efficacy of a filter device in the prevention of embolic events during carotid angioplasty and stenting: an ex vivo analysis. *J Vasc Surg* 1999;**30**:1034–44.
- ▶ This study demonstrates in an ex-vivo human model that filter protection captures only some of the debris resulting from embolisation which occurs during stenting. In fact, embolic fragments not entrapped by the filter were found both at the time of stenting and during the initial passage of the guidewire through the lesion when the filter protection was not yet inserted.
- 12 Angelini A, Reimers B, Della Barbera M, *et al*. Cerebral protection during carotid artery stenting: collection and histopathologic analysis of embolized debris. *Stroke* 2002;**33**:456–61.
- ▶ Filter protection during carotid artery stenting is able to collect atherothrombotic fragments produced by the squeezing of atherothrombotic lesions in a vast majority of cases. Collected debris consisted predominantly of thrombotic material, foam cells and cholesterol clefts. The procedure with protection was effective, feasible and safe.
- 13 Kotani J, Nanto S, Mintz GS, *et al*. Plaque gruel of atheromatous coronary lesion may contribute to the no-reflow phenomenon in patients with acute coronary syndrome. *Circulation* 2002;**106**:1672–7.
- ▶ This paper supports the concept that the no-reflow phenomenon occurring in patients with acute coronary syndromes is mainly due to a mechanical blockage of the microcirculation produced by distal embolisation of atherosclerotic plaque fragments.
- 14 Roubin GS, New G, Iyer SS, *et al*. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* 2001;**103**:532–7.
- 15 Ouriel K, Wholey MH, Fayad P, *et al*. Feasibility trial of carotid stenting with and without an embolus protection device. *J Endovasc Ther* 2005;**12**:525–37.
- 16 Angelini A, Rubartelli P, Mistrorigo F, *et al*. Distal protection with a filter device during coronary stenting in patients with stable and unstable angina. *Circulation* 2004;**110**:515–21.
- ▶ Protective devices may prevent a number of potentially unfavourable events, by limiting embolisation, thereby improving outcome. The use of protective devices, especially in lesions with higher embolic potential such

- as those which occur in older patients and in those with unstable angina, is recommended.
- 17 Limbruno U, Micheli A, De Carlo M, et al. Mechanical prevention of distal embolization during primary angioplasty: safety, feasibility, and impact on myocardial reperfusion. *Circulation* 2003;108:171–6.
 - 18 Stone GW, Webb J, Cox DA, et al. Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) Investigators. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial, *JAMA* 2005;293:1063–72.
 - ▶ Even though this randomised trial involving patients with acute myocardial infarction, with and without ST segment elevation, failed to reveal improvement in reperfusion or reduction in myocardial injury to a perceptible extent in all the patients treated with distal protection, a subgroup of patients, presenting within 6 h from the onset of pain, had a significant benefit in terms of MACE from the use of a filter wire.
 - 19 Rittersma SZ, van der Wal AC, Koch KT, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation* 2005;111:1160–5.
 - ▶ Plaque destabilisation with rupture or erosion and thrombus formation is a dynamic process which starts even weeks before the symptomatic coronary occlusion. The pathological analysis of the intracoronary thrombi, aspirated during angioplasty in patients with acute ST elevation myocardial infarction, were days or weeks old, indicating that sudden coronary occlusion is often preceded by a variable period of plaque instability and thrombus formation, initiated days or weeks before onset of symptoms.
 - 20 Mizote I, Ueda Y, Ohtani T, et al. Distal protection improved reperfusion and reduced left ventricular dysfunction in patients with acute myocardial infarction who had angioscopically defined ruptured plaque. *Circulation* 2005;112:1001–7.
 - ▶ The results of this study provide evidence that protection devices are able to reduce distal embolisation and consequent microvascular occlusion, avoiding a larger ischaemic injury and preventing left ventricular dysfunction in patients with acute myocardial infarction caused by plaque rupture.

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