Hemodynamic factors and atheromatic plaque rupture in the coronary arteries: from vulnerable plaque to vulnerable coronary segment

Demosthenes G. Katritsis[a], John Pantos[a,b] and Efstathios Efstathopoulos[b]

Coronary plaque disruption with superimposed thrombosis is the underlying pathology in the acute coronary syndromes and sudden death. Coronary plaques are constantly stressed by a variety of mechanical and hemodynamic forces that may precipitate or 'trigger' disruption of vulnerable or, at extreme conditions, even stable plaques. This paper reviews the exciting new evidence on the hemodynamic factors that may play a role in this process and provides the rationale for the introduction of the concept of the vulnerable coronary segment in the study of acute coronary syndromes. *Coron Artery Dis* 18:229–237 © 2007 Lippincott Williams & Wilkins.

Coronary Artery Disease 2007, **18**:229–237

Keywords: coronary plaque disruption, shear stress, vulnerable plaque

[a]Department of Cardiology, Athens Euroclinic and [b]Medical Physics Unit, Second Department of Radiology, University of Athens, Athens, Greece

Correspondence to Dr Demosthenes Katritsis, Department of Cardiology, Athens Euroclinic, 9 Athanassiadou Str., 115 21 Athens, Greece
Tel: +210 6416600; fax: +210 6819779;
e-mail: dkatritsis@euroclinic.gr

Received 28 July 2006 **Revised** 7 October 2006
Accepted 26 October 2006

There is now substantial evidence that the risk of plaque disruption is related to intrinsic properties of individual plaques (their vulnerability) as well as extrinsic forces acting on plaques (rupture triggers) [1,2]. The former predispose plaques to rupture, whereas the latter may precipitate disruption if vulnerable plaques are present. Coronary atherosclerosis is the most frequent cause of coronary artery disease, and coronary plaque disruption with superimposed thrombosis is the underlying pathology in the acute coronary syndromes of unstable angina, myocardial infarction, and sudden death [3,4].

The vulnerable plaque

Traditional concepts

An atheromatic plaque typically consists of two main components: a soft, lipid-rich atheromatous core and a hard, collagen-rich fibrous cap. Serial angiographic studies have indicated that the more obstructive a plaque is, the more frequently it progresses to coronary occlusion and/or gives rise to myocardial infarction [5–8]. Although an individual severe stenosis, however, becomes occluded more frequently than an individual less severe stenosis, the less obstructive plaques may give rise to more occlusions than the severely obstructive plaques at least because of their greater number [1]. Thus, coronary occlusion and myocardial infarction most frequently evolve from mild to moderate stenoses [9,10]. This has given rise to the notion that less obstructive plaques are more lipid-rich and vulnerable to rupture than larger plaques. The usually less voluminous atheromatous core was considered the more dangerous component, because it destabilizes plaques, making the fibrous cap vulnerable to rupture, and thus exposing the highly thrombogenic core to the flowing blood and leading to thrombosis [11]. Furthermore, the less severe than more severe stenoses were thought more likely to lead to acute clinical events in the case of abrupt occlusion because they are less frequently associated with protective collateral circulation [12].

Plaque rupture is the most common type of plaque complication, accounting for approximately 70% of fatal acute myocardial infarctions and/or sudden coronary deaths [13]. The so-called vulnerable plaques, that is, plaques that are prone to rupture and potential subsequent thrombosis, have been described as having the following characteristics: they are small, creating subcritical stenoses ($< 50\%$ diameter stenosis) and present features of active inflammation and endothelial denudation with superficial platelet aggregation, and have a cap thickness of $< 100\,\mu m$ and a lipid core accounting for $> 40\%$ of the plaque's total volume, or are severely stenotic with $> 90\%$ diameter stenosis [13].

Rupture of the plaque surface is followed by variable amounts of hemorrhage into the plaque and luminal thrombosis, causing sudden and rapid but often clinically silent progression of the lesion [17]. It is probably the most important mechanism underlying the episodic (vs. linear) progression of coronary lesions observed by serial angiography [4,14].

New evidence

Recent pathology studies have added further data on vulnerable plaques and have refuted the notions that even trivial plaques may rupture and that the arterial tree

0954-6928

may have such plaques in abundance [15–17]. They have demonstrated that lesions likely to be vulnerable to rupture usually are not multiple, occur more often in the proximal and middle part of major arteries and, in a large proportion of cases, may be fairly sizeable. These lesions involve at least 50% of cross-sectional vascular area in more than 80% of instances, and the necrotic cores often occupy $> 60^{\circ}$ of vessel circumferentially and 10–25% of plaque area [15–17]. Such lesions longitudinally span as long as up to 2 cm and usually assume vulnerability wherever the necrotic core is being exposed, and may only display minimal encroachment on the lumen because of positive remodeling.

Most of the acute coronary syndromes are thought to be the result of sudden luminal thrombosis [15,17–19]. Luminal thrombosis occurs from three different pathologies: plaque rupture, plaque erosion, and calcified nodules [19].

Plaque rupture is defined as a lesion consisting of a necrotic core with an overlying thin ruptured fibrous cap that leads to luminal thrombosis because of contact of platelets with a highly thrombogenic necrotic core. Pathology studies indicate that approximately 76% of all fatal coronary thrombi are precipitated by plaque rupture. The remaining 24% are caused by plaque erosion and other less well-defined mechanisms [20]. The thin-cap fibroatheroma (thin-fibrous cap that is $< 65\,\mu m$ in thickness) has been postulated to be the precursor lesion of plaque rupture and is most frequently observed in patients dying with acute plaque rupture and least frequent in plaque erosion [17]. It usually occurs with lesions showing $< 50\%$ diameter stenosis and is mostly observed in the proximal left anterior descending (LAD), left circumflex, and right coronary arteries, followed by mid and is least frequent in distal coronary arteries. Plaque erosion shows a luminal thrombus with an underlying base rich in proteoglycans and smooth muscle cells with minimal inflammation. Most erosion lesions are devoid of a necrotic core, but when present, the core does not communicate with the lumen because of a thick fibrous cap [21]. The risk factors for erosion are poorly understood and are different from those of rupture [21–23]. Usually, patients are younger than those with plaque rupture, and there is less severe narrowing at sites of thrombosis. Plaque erosion accounts for over 80% of thrombi occurring in women < 50 years of age [22]. The least common of all lesions is the calcified nodule that shows an underlying calcified plate with superimposed bony nodules that result in discontinuity of the fibrous cap and is devoid of endothelial cells with overlying luminal thrombus.

Is the location of potentially disrupted vulnerable plaques predictable?

The role of inflammation in atherosclerosis in general is now well established, and inflammatory mechanisms have been associated with vulnerable plaque rupture in several studies [24,25]. Clinical and histopathologic studies, however, have shown that active inflammation in the coronary tree of patients with acute coronary syndromes extends well beyond the site of the culprit lesion [26,27]. Indeed, both vulnerable and stable coronary plaques of patients dying of acute myocardial infarction are diffusely infiltrated by inflammatory cells [27]. Furthermore, it has been shown that disease activity has a geographic concentration – the proximal and midportions of the major coronary arteries have been shown to be the most frequent sites of plaque ruptures that result in acute coronary syndromes. The propensity for acute coronary thrombosis to occur within large epicardial arteries is well reported. In 1987, el Fawal and colleagues [28] in a pathological study on 59 patients who died of myocardial infarction in Glasgow provided evidence that thromboses are distributed in the proximal coronary vessels. Similar observations were subsequently published by other groups [29–32]. Thus, the majority of culprit lesions in ST-segment elevation myocardial infarction are located within the proximal third of the major coronary arteries [30]. Coronary stenoses of $> 50\%$ of luminal diameter involve most frequently the proximal portion of the major coronary arteries [31,32]. The proximal lesions are long and diffuse, whereas distal lesions are more often short and discrete [31]. In young patients < 40 years, dying of noncardiovascular causes, coronary plaques are concentrated proximally and diminish with distance in all the coronary arteries [29]. These observations suggest that the proximal coronary plaques are more prone to rupture. Recently, Wang and colleagues [33] demonstrated that acute coronary occlusions leading to myocardial infarction tend to cluster in predictable 'hot spots' within the proximal third of the coronary arteries, particularly the LAD and left circumflex. Recent pathology studies have also demonstrated that over 50% of thin cap fibroatheromatic plaques occur in the proximal portions of the major coronary arteries, another one-third in the midportion of these arteries, and the rest are distributed in distal segments [17]. A similar distribution has been found in ruptures and healed plaque ruptures [17]. The most frequent location for both erosion and rupture was the proximal LAD artery (66%) followed by the right (18%) and the left circumflex (14%) [17]. These observations suggest that high-probability zones of coronary thrombosis may exist along the coronary tree. Thus, the susceptibility to atherothrombosis differs not only among individuals with similar risk factor scores (individual susceptibility), but also among different arterial segments from the same individual (arterial susceptibility).

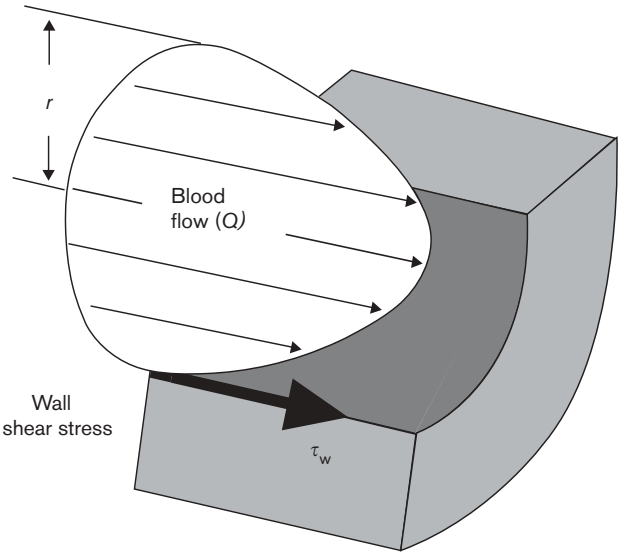
Hemodynamic factors triggering plaque disruption

Substantial evidence now exists that the risk of plaque disruption is related to intrinsic properties of individual

plaques (their vulnerability) as well as extrinsic forces acting on plaques (rupture triggers) [1,2]. The former predispose plaques to rupture, whereas the latter may precipitate disruption if vulnerable plaques are present. As discussed previously, pathoanatomic examination of intact and disrupted plaques and in-vitro mechanical testing of isolated fibrous caps from aorta indicate that vulnerability to rupture depends on the size and consistency of the atheromatous core, the thickness and collagen content of the fibrous cap, and local inflammation within the cap. Other factors such as a thrombotic tendency owing to platelet hyperaggregability, hypercoagulability, and/or impaired fibrinolysis are important in the presence of previously disrupted plaques for the formation of an occluding thrombus [13]. Most of the efforts of the cardiology community up to now have focused on systemic therapies for stabilization of atheromatic plaques along the coronary tree [34].

Coronary plaques, however, are constantly stressed by a variety of mechanical and hemodynamic forces that may precipitate or 'trigger' disruption of vulnerable or, under extreme conditions, even stable plaques. Surges in sympathetic activity with a sudden increase in blood pressure, pulse rate, heart contraction, and coronary blood flow, and changes in vascular tone may affect plaque integrity along the coronary tree [1,17]. Several hemodynamic factors may play a role in this process.

Fig. 1



Cross-sectional diagram of a vessel illustrating wall shear stress τ_w, the frictional force per unit area that is exerted by the flowing viscous blood. In the case of laminar flow at a straight part of the vessel it can be shown that $\tau_w = \frac{4\mu Q}{\pi r^3}$ where μ is the dynamic viscosity of blood, Q the flow, and r the radius of the vessel (Poiseuille's law).

Wall shear stress

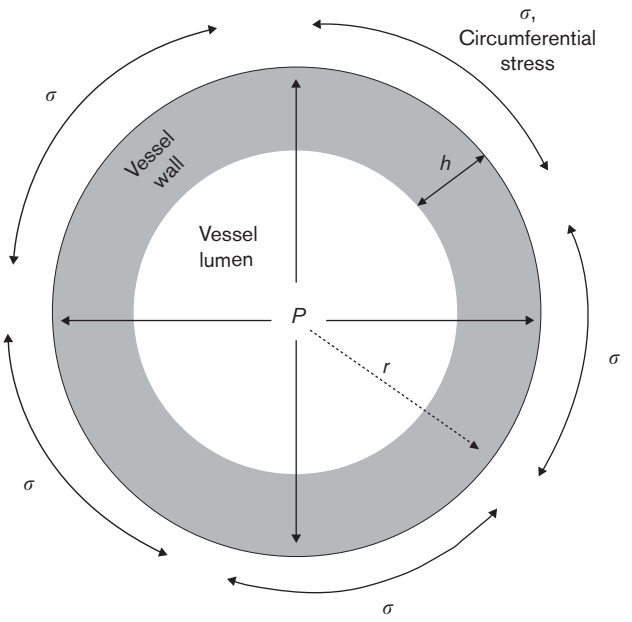
Wall shear stress is the tangential force per unit area that is exerted by the flowing blood on the surface of the conduit blood vessel. Shear stress results from the viscosity of blood, which is a kind of internal friction between the adjacent layers of the flowing blood [35] (Fig. 1).

Following the initial controversial reports on the role of shear stress on atheromatosis, the prevailing theory nowadays is the one proposed by Caro and colleagues [36,37], which relates the atheromatic process with low shear stress. This is based on the hypothesis that the accumulation of lipoproteins on the arterial intima is because of the pathological mass transfer between blood and arterial wall as a result of low shear stress. Subsequent observations and studies have validated the low shear stress hypothesis of atherosclerosis [38–41] and have revealed that atherogenesis preferentially involves the outer walls of vessel bifurcations, side branches and regions of high curvature in the arterial tree [38,42,43]. In these geometrically predisposed locations, vessel wall shear stress is significantly lower in magnitude and exhibits directional changes and flow separation, features absent from regions of the arterial tree that are generally spared from atherosclerosis [42–46]. Although the relationship between wall shear stress and development of atherosclerosis seems rather established its potential effect on plaque rupture has not been studied extensively.

The magnitude of wall shear stress is inversely proportional to the cube of the artery radius [35,47]. Therefore, a small change in the radius of the artery will produce a large change in wall shear stress. In reality, flow into a stenotic zone will increase wall shear stress more than that anticipated by the change of radius alone because the acceleration of blood into a stenosis flattens the parabolic velocity profile, leading to a much more rapid increase in blood velocity adjacent to the vessel wall and thus increased wall shear stress [48]. It seems that the wall shear stress at a 50% subcritical stenosis is within the range of shear forces hypothesized to be capable of inducing endothelial damage [49]. The fact that shear forces induce marked endothelial damage does not prove that they are capable of causing plaque rupture. Intimal damage, even if initially of minimal mural depth, however, may increase the likelihood of rupture at sites of increased wall shear stress [50]. Observations of regression of graft hyperplasia stimulated by high shear stress in nonatherosclerotic baboons indicate that high shear stress stimulates the endothelium to induce thinning of the fibrous cap [51]. At the cap shoulders this effect might even be enhanced by the synergistic action of high shear stress and cyclic strain that preserves the endothelium [52] and increases nitric oxide (NO)

production [53], which might lead to suppression of smooth muscle cell proliferation and matrix synthesis [54]. At the upstream plaque shoulders shear stress is high, and as plaque rupture occurs most frequently upstream, it has been postulated that high shear stress might be the dominant factor [55]. At the downstream plaque shoulders, shear stress is low and this could lead to substantial endothelial cell apoptosis [56] and progression of atherosclerosis [57] but low risk of plaque rupture. The mechanobiologic effect of shear stress, however, is also dominant at the midcap [55], and clinical studies have revealed that the pattern of plaque rupture may depend on several factors. Richardson and colleagues [58] have shown that fatal plaque ruptures were more frequently observed in the lateral cap shoulders than in midcap regions of the plaque. In a subsequent study on people who had suffered fatal infarctions during exercise, plaque ruptures were mostly located in the midcap regions, as opposed to the higher prevalence of ruptures in the lateral cap shoulders in patients who died at rest [59]. Thus, plaque rupture is a complex process being affected by several additional factors such as blood pressure and circumferential stress.

Fig. 2



Cross-section of an artery illustrating circumferential tensile stress (σ) at the vessel wall, which balances the transmural blood pressure (P). If the thickness of the vessel wall (h) is small compared with the vessel radius (r) it can be shown that $\sigma = \frac{Pr}{h}$.(Laplace's law).

Circumferential wall stress

The circumferential wall stress is a tensile stress that is induced on the vessel wall by the transmural blood pressure, and is several orders of magnitude stronger than the wall shear stress [55] that is a tangential stress induced by the flowing blood owing to its viscosity. The blood pressure inside a vessel exerts a circumferential force across the vessel wall, which must be counteracted by a tensile stress within the vessel wall to keep the vessel intact [48]. This tensile stress is described by the law of Laplace and is correlated with luminal pressure and diameter and is inversely related to the thickness of the wall, assuming that the vessel represents a thin-walled, axisymmetric cylinder [48,60] (Fig. 2).

Increasing plaque volume increases the thickness of the wall and decreases the luminal diameter (unless there is vessel remodeling), thereby leading to decrease in the circumferential stress in the atherosclerotic plaque. Therefore, the tensile stress created in fibrous caps of mildly or moderately stenotic plaques is greater than that created in caps of severely stenotic plaques with the same cap thickness and exposed to the same blood pressure. For a given intraluminal pressure, the circumferential stress on a 50% stenosis is five times greater than on a 90% stenosis [48]. Consequently, mildly or moderately stenotic plaques are generally stressed more than severely stenotic plaques and could therefore be more prone to rupture [61,62]. Cheng and colleagues [61], in an elegant pathology study, have shown that plaques rupture near regions of high tensile circumferential stress and that these stresses are higher than those found in stable lesions. Calcification, as opposed to lipid plaque content, does not appear to be correlated to circumferential stress [63]. Thus, coronary artery calcifications do not significantly affect the stability of atheroma, in contrast to the significant reduction of stability associated with lipid. In another experimental study on vessel models, increased plaque volume or severity of stenosis resulted in decreased stress concentration [60]. When the plaque thickness remained constant, expansive remodeling, which is frequently observed as a compensatory process, led to greater concentration of stress than did constrictive remodeling [60].

Surges and drops in intraluminal blood pressure

Constantinides and Lawder [64,65] reported that, in animals with advanced atherosclerosis, thrombi over hemorrhagic plaques could be produced by intravenous injection of a combination of an endotheliotoxic agent (Russell viper venom) and vasoactive agents. It was hypothesized, therefore, that plaque fissures can be produced in mammalian atherosclerotic arteries by a sudden surge of intraluminal pressure in synergy with endothelial damage [66]. An agent such as Russell viper venom, however, can cause endothelial damage and might contribute to plaque rupture by itself; thus the evidence of increased intraluminal pressure as a factor in the initiation of plaque rupture provided by this study is questionable [50].

Blood pressure drops over a lesion under conditions of high blood flow might also act as triggers of plaque rupture as they induce peaks in axial tensile stress [67]. Such a pressure drop might deform a vulnerable plaque and induce substantial axial strain [55]. Calculations by computational fluid dynamics coupled to solid-deformation mechanics to a symmetric lesion model showed that a relatively small (20 mmHg) pressure drop can induce more than 10 kPa axial tensile stress in a 75-μm-thick cap [55]. Given that the average minimum cap in people who died after exertion was 5.6 mm [59], the above model predicts that the cap would be loaded with a peak tensile stress of 134 kPa [55]. The fracture stresses reported for caps covering lipid pools in human aortic tissue samples have been reported as 75 kPa for nonulcerated plaques and 20 kPa for ulcerated plaques [68]; thus the stress induced by the pressure drop far exceeds the stress required to rupture an atherosclerotic plaque. This finding might explain why plaques rupture at the midcap (75%) was the most frequent cause of death (68%) of people who died during exertion [59]. By contrast, in people who died at rest, rupture explained only 23% of the cases and mostly occurred at the plaque shoulders (65%) [59]. A more likely trigger of plaque rupture in this case is a blood pressure surge [55]. The predictive nature of a steep stenosis-outlet geometry for infarction, which is attributed to increased distal thrombogenicity [69], might also be related to the larger blood pressure drop over such a stenosis [55].

Mechanical shear failure

Mechanical shear stress is the shearing stress that is exerted between adjacent layers of the vessel induced by the circumferential elongation owing to circumferential stresses. Mechanical shear failure of the vessel occurs when vessel layers separate and slide relative to one another and when the extracellular matrix, which functions as the glue holding these layers together, cannot withstand the shear stress [2]. Mechanical shear stress may develop in plaques at the interface between tissues of different stiffness, resulting in mechanical shear failure [1]. Calcified plates and adjacent noncalcified tissue, for example, may slide against each other, 'shearing' plaques apart [2,70]. Mechanical shear stress and circumferential stress may participate in the same catastrophic vascular event as regions with high mechanical shear stresses are frequently found at locations with high-circumferential tensile stress [2].

Arterial wall collapse

A mechanism that can possibly affect the integrity of plaques is arterial wall collapse caused by arterial stenosis. It is well known that arteries, being thin-walled elastic tubes, are collapsible [71]. According to the Bernoulli principle, at sites of artery stenosis, blood flow causes a drop in static pressure within the throat of the stenosis [72]. As flow velocity increases through a stenosis, the static pressure falls proportionally to the velocity squared. With high-grade stenosis, static pressure in the throat of the stenosis may become less than the external surrounding pressure of the artery, causing a negative transmural pressure which tends to cause collapse of the vessel [73,74]. The collapse of arteries may produce highly compressive stresses from the possible buckling of the wall [73]. As arteries are typically constructed for tension only, compressive stress is particularly determinant in that it may induce a crack or cavity to grow leading to mechanical fatigue [73]. Additionally, the strains associated with buckling are much larger than that normally encountered during pulsatile pressure expansion. These large strains may additionally contribute to mechanical fatigue of the plaque cap [73]. Arterial wall collapse may be partially responsible for plaque fracture. It is also possible that collapse of the artery may injure the endothelium, thereby promoting thrombus formation [74]. The resultant wall motion and oscillation during partial collapse may have a bearing on the etiology of intraplaque hemorrhage, plaque ulceration, angiographically observed 'spasm', and poststenotic dilation [74].

Circumferential bending

The propagating pulse wave causes cyclic changes in lumen size and shape with deformation and bending of plaques, particularly the soft ones. For normal compliant arteries, the cyclic diastolic–systolic change in lumen diameter is about 10% [2], but it becomes smaller with age and during atherogenesis because of the increase in stiffness [75]. Generally, concentric plaques do not change as much during the cardiac cycle as eccentric plaques do. The latter typically bend at their edges, that is, at the junction between the stiff plaque and the more compliant plaque-free vessel wall. Cyclic bending may, in the long term, weaken the plaque and lead to spontaneous fatigue disruption, whereas a sudden accentuated bending may trigger rupture of a weakened plaque [1].

Longitudinal flexion

Coronary arteries, particularly the LAD coronary artery, tethered to the surface of the beating heart undergo cyclic longitudinal deformations by axial bending (flexion) and stretching [1]. Approximately 40 million flexions of the coronary arteries occur during 1 year [76]. Angiographically, the angle of flexion was recently found to correlate with subsequent lesion progression, but the coefficient of correlation was low [76]. Like circumferential bending, a sudden accentuated longitudinal flexion may trigger plaque disruption, whereas long-term cyclic flexion may fatigue and weaken the plaque [1]. The effect of local stress on the normal and diseased moving arterial wall with lipid pool and plaque cap was investigated in a patient-specific 3D coronary arterial tree reconstruction by finite element analysis [77,78]. A large value of stress gradient was found at bifurcation regions indicating that higher stress occurs at junction

between the proceeding and branching vessels during cyclic flexion [77,78]. Additionally, the regions closer to the bifurcations underwent a larger deformation, yielding a higher stress than those further from the bifurcations. It seems that when the length of the lesion increases by 100% the maximum plaque stress increases by 10–30% and the stress concentration becomes less localized, whereas when the diameter of the vessel is reduced to half of its size, the maximum stress dramatically increases by 300–400% and the stress gradient becomes higher [79]. These findings are in keeping with the observation that plaque rupture frequently occurs in the location at which the geometry of the artery is subject to considerable transformation [79].

Vasospasm

Angiographic studies have identified spasm in coronary arteries at, and in close proximity to, sites of severe luminal narrowing [50]. It is suggested that sites of atherosclerotic narrowing may be hypercontractile because of possible loss of endothelial-dependent arterial relaxation associated with structural or functional damage of these cells [50]. Vasospasm could theoretically rupture plaques by compressing the atheromatous core and 'blowing' the fibrous cap out into the lumen [1]. Plaque disruption and vasospasm indeed frequently coexist [80,81] but it is more likely that the former gives rise to the latter than vice versa [80,82–84]. Onset of myocardial infarction is uncommon during or shortly after drug-induced spasm of even severely diseased coronary arteries [85,86], indicating that spasm rarely, if ever, precipitates plaque disruption and/or luminal thrombosis [1]. Furthermore, spasmolytic drugs have never proved effective in preventing myocardial infarction in patients with vasospastic angina [1]. Vasospasm might also be involved in the pathophysiology of erosion [17]. This hypothesis is based on the observation that there is lack of endothelium and the media in these segments is intact and is thicker than at sites of plaque rupture [87]. Plaque erosions tend to embolize more frequently than plaque rupture (74 vs. 40%, respectively) [17]. Vasospasm might also produce 'volcano-like eruptions' of lipid from ruptured plaques [88].

Fatigue failure

A fatigue process is an incremental failure progression under the influence of repetitive biomechanical stresses, which result in acute failure at pressure levels seemingly much lower than the tissue strength [89]. Fatigue has been mentioned as a mechanism that might play a role in plaque rupture as the cardiovascular system is a classic fatigue environment: at a heart rate of 70 beats/min, arterial tissues are subjected to over 36 million stress cycles per year [89]. Plaque rupture, therefore, can be considered as a catastrophic event that occurs in the setting of prolonged cyclic stress from arterial pressure waves [90]. Bank and colleagues [90] have summarized the physiologic and epidemiologic data consistent with the concept of fatigue as a critical biomechanical factor in plaque rupture: (i) atherosclerotic plaque rupture occurs at stress levels much lower than those needed to rupture the plaque with a single maximal stress, (ii) atherosclerotic plaques rupture predominantly at locations of stress concentration, (iii) atherosclerotic plaque rupture often occurs suddenly and without warning, (iv) cardiovascular disease is associated with increased resting heart rate, (v) cardiovascular events are correlated with pulse pressure, which is directly proportional to the stress amplitude impacting upon the arterial wall, and (vi) a well-established risk factor for myocardial infarction is increased mean arterial pressure, which results in increased plaque stress.

From fatigue research it is known that fatigue life can often be divided into three periods: crack initiation, stable crack propagation, and final rupture [91]. Endothelial erosion which is well known to occur at an early stage in the atherosclerosis process is increasingly recognized as an important mechanism leading to acute coronary syndromes and may play a role in the initiation stage of the fatigue process [89]. The initiation period, however, is the most difficult to predict and it is more affected by biological and biochemical factors such as inflammation, healing and sedimentation than the two ensuing fatigue stages [89]. Probably of more importance is the intermediate period of stable crack propagation because incomplete ruptures are potentially detectable [89]. As rupture, however, has been regarded as an acute event, neither has the detection of incomplete rupture been part of screening procedures nor are the diagnostic systems designed to detect partial rupture [89]. The final rupture is the shortest phase of fatigue and it usually occurs abruptly and without warning, such as experienced in myocardial infarction [89]. Fatigue failure as the cause of plaque rupture contrasts sharply with the triggering theory, which suggests that hemodynamic changes resulting from emotional or physical stress provoke plaque rupture [90]. According to the fatigue failure hypothesis, these triggers simply cause plaques already close to rupturing to complete their fatigue life by sudden failure [90].

Rupture of the vasa vasorum

Rupture of the coronary vasa vasorum may play a role in the onset or triggering of myocardial infarction. It has been shown that the direction of flow in these fragile vessels is inward from the adventitial vasa vasorum through the media into the thickened intima, rather than outward from the coronary lumen [92]. It has been also shown that vasa vasorum blood flow in the region of atherosclerotic plaques is increased five-fold over that observed in the normal media [93]. The increased blood flow implies a large inward (lumen-directed) pressure

gradient in the stenosed region of the coronary artery [94]. The luminal blood flow creates a region of low pressure centered in the narrowest point of the stenosis according to the Bernoulli principle, whereas the vasa vasorum arise upstream in a high-pressure region [94]. Plaque rupture may occur from the inside (from the plaque into the lumen) as, under certain conditions, the pressure at these capillary vessels could exceed that in the coronary lumen distal to the stenosis, leading to explosive rupture of the plaque into the lumen [95]. Davies and Thomas [96] have found that tiny areas of bleeding are frequent at the base of advanced lesions; however, a small capillary is difficult to disrupt a fibrous cap against the much higher luminal pressure [97]. This scenario could occur occasionally in some rare instances but it is not common because it is difficult to reconcile with hard histologic evidence in this area [97].

Asynchronous hemodynamics

A unique hemodynamic feature is present at the coronaries: the wall shear stress induced by blood flow and circumferential strain driven by pressure are highly out-of-phase temporally (asynchronous hemodynamics). A recent study demonstrated a correlation between asynchronous hemodynamics and proatherogenic gene expression patterns *in vivo* that is induced by hemodynamics inherent to the circulation [98]. The potential role of this phenomenon in plaque rupture is not known.

From vulnerable plaque to vulnerable segment

Coronary plaque rupture is a complex process of multifactorial nature that is not yet fully understood. Hemodynamic factors appear to play a significant role in coronary plaque disruption and consequent unstable coronary syndromes and myocardial infarction. Apart from arterial pressure and heart rate, however, coronary fluid dynamics is also dependent on specific anatomic and morphological parameters throughout the cardiac cycle. Evidence is observed that particular segments of the coronary arteries may be more susceptible to atherothrombosis than others. This inevitably introduces the concept of the vulnerable segment as a logical approach toward the identification of patients at high risk for an acute coronary event. Such a view should explain why some typically vulnerable plaques according to pathological criteria are not associated with rupture [98]. Furthermore, it provides the rationale to explain the observation that certain plaques may rupture but do not result in thrombosis. Flow parameters may play a role in this phenomenon.

Potential identification of these high-risk zones along the coronary tree should be of paramount clinical importance for locally directed preventive strategies [99,100]. Further in-vitro and in-vivo studies and in-depth analysis of coronary hemodynamics are necessary for characterization and identification of such vulnerable segments.

Conclusions

1. Major determinants of vulnerability of a plaque to rupture are size and consistency of the atheromatous core, thickness of the fibrous cap covering the core, and ongoing inflammation within the cap.
2. Plaque disruption tends to occur at points at which the plaque surface is weakest and most vulnerable, which coincide with points at which stresses resulting from biomechanical and hemodynamic forces acting on plaques are concentrated.
3. A comprehensive analysis of hemodynamic factors and their potential effect on plaque formation and rupture has not been carried out and anatomical and morphological criteria for the coronary arteries are relevant in this respect.
4. Such an analysis might indicate segments of the coronary arteries, vulnerable coronary segments, at which plaques are more susceptible to rupture, and which, therefore, represent potential sites of therapeutic intervention.

References

1 Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92**:657–671.
2 Lee RT, Kamm RD. Vascular mechanics for the cardiologist. *J Am Coll Cardiol* 1994; **23**:1289–1295.
3 Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med* 1992; **326**:242–250.
4 Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. *Heart* 1999; **82**:265–268.
5 Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, *et al.* Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the coronary artery surgery study (CASS). CASS participating investigators and staff. *J Am Coll Cardiol* 1993; **22**:1141–1154.
6 Ellis S, Alderman E, Cain K, Fisher L, Sanders W, Bourassa M. Prediction of risk of anterior myocardial infarction by lesion severity and measurement method of stenoses in the left anterior descending coronary distribution: a CASS registry study. *J Am Coll Cardiol* 1988; **11**:908–916.
7 Giroud D, Li JM, Urban P, Meier B, Rutishauer W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992; **69**:729–732.
8 Kaski JC, Chester MR, Chen L, Katritsis D. Rapid angiographic progression of coronary artery disease in patients with angina pectoris. The role of complex stenosis morphology. *Circulation* 1995; **92**:2058–2065.
9 Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, *et al.* Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988; **12**:56–62.
10 Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, *et al.* Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988; **78**:1157–1166.
11 Fernandez-Ortiz A, Badimon JJ, Falk E, Fuster V, Meyer B, Mailhac A, *et al.* Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J Am Coll Cardiol* 1994; **23**:1562–1569.
12 Danchin N. Is myocardial revascularisation for tight coronary stenoses always necessary? *Lancet* 1993; **342**:224–225.
13 Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, *et al.* From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation* 2003; **108**: 1664–1672.

14 Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J, *et al*. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. *Circulation* 2001; **103**:934–940.

15 Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol* 2006; **47**: C7–C12.

16 Narula J, Willerson JT. Prologue: detection of vulnerable plaque. *J Am Coll Cardiol* 2006; **47**:13–18.

17 Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006; **47**:C13–C18.

18 Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995; **92**:1701–1709.

19 Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 2000; **20**:1262–1275.

20 Falk E, Shah PK, Fuster V. Atherothrombosis and thrombosis-prone plaques. In: Fuster V, Alexander RW, O'Rourke RA, *et al*., editors. *Hurst's the heart*. 11th ed. New York, NY: McGraw-Hill; 2004. pp. 1123–1139.

21 Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, *et al*. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996; **93**:1354–1363.

22 Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* 1998; **97**:2110–2116.

23 Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997; **336**:1276–1282.

24 Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: Part I: evolving concepts. *J Am Coll Cardiol* 2005; **46**:937–954.

25 Libby P. Inflammation in atherosclerosis. *Nature* 2002; **420**:868–874.

26 Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. *N Engl J Med* 2002; **347**:5–12.

27 Mauriello A, Sangiorgi G, Fratoni S, Palmieri G, Bonanno E, Anemona L, *et al*. Diffuse and active inflammation occurs in both vulnerable and stable plaques of the entire coronary tree: a histopathologic study of patients dying of acute myocardial infarction. *J Am Coll Cardiol* 2005; **45**:1585–1593.

28 El Fawal MA, Berg GA, Wheatley DJ, Harland WA. Sudden coronary death in Glasgow: nature and frequency of acute coronary lesions. *Br Heart J* 1987; **57**:329–335.

29 Fox B, James K, Morgan B, Seed A. Distribution of fatty and fibrous plaques in young human coronary arteries. *Atherosclerosis* 1982; **41**:337–347.

30 Gibson CM, Kirtane AJ, Murphy SA, Karha J, Cannon CP, Giugliano RP, *et al*. Distance from the coronary ostium to the culprit lesion in acute ST-elevation myocardial infarction and its implications regarding the potential prevention of proximal plaque rupture. *J Thromb Thrombolysis* 2003; **15**:189–196.

31 Hochman JS, Phillips WJ, Ruggieri D, Ryan SF. The distribution of atherosclerotic lesions in the coronary arterial tree: relation to cardiac risk factors. *Am Heart J* 1988; **116**:1217–1222.

32 Vieweg WV, Alpert JS, Johnson AD, Dennish GW, Nelson DP, Warren SE, *et al*. Distribution and severity of coronary artery disease in 500 patients with angina pectoris. *Cathet Cardiovasc Diagn* 1979; **5**:319–330.

33 Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 2004; **110**:278–284.

34 Ambrose JA, D'Agate DJ. Classification of systemic therapies for potential stabilization of the vulnerable plaque to prevent acute myocardial infarction. *Am J Cardiol* 2005; **95**:379–382.

35 Milnor W. *Hemodynamics*. Baltimore/London: Williams & Wilkins; 1982.

36 Caro CG, Fitz-Gerald JM, Schroter RC. Atheroma and arterial wall shear. Observation, correlation and proposal of a shear dependent mass transfer mechanism for atherogenesis. *Proc R Soc Lond B Biol Sci* 1971; **177**:109–159.

37 Caro CG, Fitz-Gerald JM, Schroter RC. Proposal of a shear dependent mass transfer mechanism for atherogenesis. *Clin Sci* 1971; **40**:5P.

38 Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. *Circ Res* 1990; **66**:1045–1066.

39 Bharadvaj BK, Mabon RF, Giddens DP. Steady flow in a model of the human carotid bifurcation. Part I – flow visualization. *J Biomech* 1982; **15**:349–362.

40 Motomiya M, Karino T. Flow patterns in the human carotid artery bifurcation. *Stroke* 1984; **15**:50–56.

41 Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. *Circ Res* 1983; **53**:502–514.

42 Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev* 1995; **75**:519–560.

43 Resnick N, Yahav H, Shay-Salit A, Shushy M, Schubert S, Zilberman LC, *et al*. Fluid shear stress and the vascular endothelium: for better and for worse. *Prog Biophys Mol Biol* 2003; **81**:177–199.

44 Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999; **282**:2035–2042.

45 Benson TJ, Nerem RM, Pedley TJ. Assessment of wall shear stress in arteries, applied to the coronary circulation. *Cardiovasc Res* 1980; **14**:568–576.

46 Pantos J, Efstathopoulos E, Katritsis D. Vascular wall shear stress in clinical practice. *Curr Vasc Pharmacol* (in press).

47 Nichols W, O'Rourke M. *McDonald's blood flow in arteries: theoretical, experimental and clinical principles*. London: Hodder Arnold; 2005.

48 MacIsaac AI, Thomas JD, Topol EJ. Toward the quiescent coronary plaque. *J Am Coll Cardiol* 1993; **22**:1228–1241.

49 Fry DL. Acute vascular endothelial changes associated with increased blood velocity gradients. *Circ Res* 1968; **22**:165–197.

50 Gertz SD, Roberts WC. Hemodynamic shear force in rupture of coronary arterial atherosclerotic plaques. *Am J Cardiol* 1990; **66**:1368–1372.

51 Mattsson EJ, Kohler TR, Vergel SM, Clowes AW. Increased blood flow induces regression of intimal hyperplasia. *Arterioscler Thromb Vasc Biol* 1997; **17**:2245–2249.

52 Haga M, Chen A, Gortler D, Dardik A, Sumpio BE. Shear stress and cyclic strain may suppress apoptosis in endothelial cells by different pathways. *Endothelium* 2003; **10**:149–157.

53 Casey PJ, Dattilo JB, Dai G, Albert JA, Tsukurov OI, Orkin RW, *et al*. The effect of combined arterial hemodynamics on saphenous venous endothelial nitric oxide production. *J Vasc Surg* 2001; **33**:1199–1205.

54 Kolpakov V, Gordon D, Kulik TJ. Nitric oxide-generating compounds inhibit total protein and collagen synthesis in cultured vascular smooth muscle cells. *Circ Res* 1995; **76**:305–309.

55 Slager CJ, Wentzel JJ, Gijsen FJ, Thury A, van der Wal AC, Schaar JA, *et al*. The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. *Nat Clin Pract Cardiovasc Med* 2005; **2**:456–464.

56 Tricot O, Mallat Z, Heymes C, Belmin J, Leseche G, Tedgui A. Relation between endothelial cell apoptosis and blood flow direction in human atherosclerotic plaques. *Circulation* 2000; **101**:2450–2453.

57 Slager CJ, Wentzel JJ, Gijsen FJ, Schuurbiers JC, van der Wal AC, van der Steen AF, *et al*. The role of shear stress in the generation of rupture-prone vulnerable plaques. *Nat Clin Pract Cardiovasc Med* 2005; **2**:401–407.

58 Richardson PD, Davies MJ, Born GV. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989; **ii**:941–944.

59 Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. *JAMA* 1999; **281**:921–926.

60 Imoto K, Hiro T, Fujii T, Murashige A, Fukumoto Y, Hashimoto G, *et al*. Longitudinal structural determinants of atherosclerotic plaque vulnerability: a computational analysis of stress distribution using vessel models and three-dimensional intravascular ultrasound imaging. *J Am Coll Cardiol* 2005; **46**:1507–1515.

61 Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions. A structural analysis with histopathological correlation. *Circulation* 1993; **87**:1179–1187.

62 Richardson PD. Biomechanics of plaque rupture: progress, problems, and new frontiers. *Ann Biomed Eng* 2002; **30**:524–536.

63 Huang H, Virmani R, Younis H, Burke AP, Kamm RD, Lee RT. The impact of calcification on the biomechanical stability of atherosclerotic plaques. *Circulation* 2001; **103**:1051–1056.

64 Constantinides P. *Experimental atherosclerosis*. New York: Elsevier Publishing; 1965.

65 Constantinides P, Lawder J. Experimental thrombosis and hemorrhage in atherosclerotic arteries. *Fed Proc* 1963; **22**:251–259.

66 Constantinides P. Plaque fissures in human coronary thrombosis. *J Atheroscler Res* 1966; **6**:1–17.

67 Doriot PA. Estimation of the supplementary axial wall stress generated at peak flow by an arterial stenosis. *Phys Med Biol* 2003; **48**:127–138.

68 Burleigh MC, Briggs AD, Lendon CL, Davies MJ, Born GV, Richardson PD. Collagen types I and III, collagen content, GAGs and mechanical strength of human atherosclerotic plaque caps: span-wise variations. *Atherosclerosis* 1992; **96**:71–81.

69 Ledru F, Theroux P, Lesperance J, Laurier J, Ducimetiere P, Guermonprez JL, *et al*. Geometric features of coronary artery lesions favoring acute occlusion and myocardial infarction: a quantitative angiographic study. *J Am Coll Cardiol* 1999; **33**:1353–1361.

70 Berliner JA, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, *et al*. Atherosclerosis: basic mechanisms. Oxidation, inflammation, and genetics. *Circulation* 1995; **91**:2488–2496.

71 Shapiro AH. Steady flow in collapsible tubes. *J Biomech Eng* 1977; **99**:126–147.

72 Pedley TJ. *The fluid mechanics of large blood vessels*. Cambridge: Cambridge University Press; 1980.

73 Aoki T, Ku DN. Collapse of diseased arteries with eccentric cross section. *J Biomech* 1993; **26**:133–142.

74 Binns RL, Ku DN. Effect of stenosis on wall motion. A possible mechanism of stroke and transient ischemic attack. *Arteriosclerosis* 1989; **9**:842–847.

75 Alfonso F, Macaya C, Goicolea J, Hernandez R, Segovia J, Zamorano J, *et al*. Determinants of coronary compliance in patients with coronary artery disease: an intravascular ultrasound study. *J Am Coll Cardiol* 1994; **23**:879–884.

76 Stein PD, Hamid MS, Shivkumar K, Davis TP, Khaja F, Henry JW. Effects of cyclic flexion of coronary arteries on progression of atherosclerosis. *Am J Cardiol* 1994; **73**:431–437.

77 Wu HC, Chen SY, Carroll JD. Stress analysis on 3D coronary arterial tree and plaque subject to cyclic flexion. In: *Summer Bioengineering Conference*. Florida; 2003.

78 Wu HC, Chen SY, Shroff SG, Carroll JD. Stress analysis using anatomically realistic coronary tree. *Med Phys* 2003; **30**:2927–2936.

79 Salzar RS, Thubrikar MJ, Eppink RT. Pressure-induced mechanical stress in the carotid artery bifurcation: a possible correlation to atherosclerosis. *J Biomech* 1995; **28**:1333–1340.

80 Bogaty P, Hackett D, Davies G, Maseri A. Vasoreactivity of the culprit lesion in unstable angina. *Circulation* 1994; **90**:5–11.

81 Etsuda H, Mizuno K, Arakawa K, Satomura K, Shibuya T, Isojima K. Angioscopy in variant angina: coronary artery spasm and intimal injury. *Lancet* 1993; **342**:1322–1324.

82 Golino P, Ashton JH, Buja LM, Rosolowsky M, Taylor AL, McNatt J, *et al*. Local platelet activation causes vasoconstriction of large epicardial canine coronary arteries in vivo. Thromboxane A2 and serotonin are possible mediators. *Circulation* 1989; **79**:154–166.

83 Lam JY, Chesebro JH, Steele PM, Badimon L, Fuster V. Is vasospasm related to platelet deposition? Relationship in a porcine preparation of arterial injury in vivo. *Circulation* 1987; **75**:243–248.

84 Zeiher AM, Schachinger V, Weitzel SH, Wollschlager H, Just H. Intracoronary thrombus formation causes focal vasoconstriction of epicardial arteries in patients with coronary artery disease. *Circulation* 1991; **83**:1519–1525.

85 Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, *et al*. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982; **65**:1299–1306.

86 Kaski JC, Tousoulis D, McFadden E, Crea F, Pereira WI, Maseri A. Variant angina pectoris. Role of coronary spasm in the development of fixed coronary obstructions. *Circulation* 1992; **85**:619–626.

87 Kolodgie FD, Burke AP, Farb A, Gold HK, Yuan J, Narula J, *et al*. The thin-cap fibroatheroma: a type of vulnerable plaque. The major precursor lesion to acute coronary syndromes. *Curr Opin Cardiol* 2001; **16**:285–292.

88 Lin CS, Penha PD, Zak FG, Lin JC. Morphodynamic interpretation of acute coronary thrombosis, with special reference to volcano-like eruption of atheromatous plaque caused by coronary artery spasm. *Angiology* 1988; **39**:535–547.

89 Versluis A, Bank AJ, Douglas WH. Fatigue and plaque rupture in myocardial infarction. *J Biomech* 2006; **39**:339–347.

90 Bank AJ, Versluis A, Dodge SM, Douglas WH. Atherosclerotic plaque rupture: a fatigue process? *Med Hypotheses* 2000; **55**:480–484.

91 Ewalds HL, Wanhill RJH. *Fracture mechanics*. Delft: Edward Arnold; 1985.

92 Barger AC, Beeuwkes R 3rd, Lainey LL, Silverman KJ. Hypothesis: vasa vasorum and neovascularization of human coronary arteries. A possible role in the pathophysiology of atherosclerosis. *N Engl J Med* 1984; **310**: 175–177.

93 Heistad DD, Armstrong ML. Blood flow through vasa vasorum of coronary arteries in atherosclerotic monkeys. *Arteriosclerosis* 1986; **6**:326–331.

94 Barger AC, Beeuwkes R 3rd. Rupture of coronary vasa vasorum as a trigger of acute myocardial infarction. *Am J Cardiol* 1990; **66**: 41G–43G.

95 Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989; **79**:733–743.

96 Davies MJ, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. *N Engl J Med* 1984; **310**:1137–1140.

97 Constantinides P. Cause of thrombosis in human atherosclerotic arteries. *Am J Cardiol* 1990; **66**:37G–40G.

98 Dancu MB, Tarbell JM. Coronary endothelium expresses a pathologic gene pattern compared to aortic endothelium: correlation of asynchronous hemodynamics and pathology in vivo. *Atherosclerosis* 2006; [Epub ahead of print].

99 Meier B, Ramamurthy S. Plaque sealing by coronary angioplasty. *Cathet Cardiovasc Diagn* 1995; **36**:295–297.

100 Meier B. Plaque sealing by coronary angioplasty. *Heart* 2004; **90**: 1395–1398.