

# Statins and perioperative myocardial infarction.

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## ABSTRACT

The growing prevalence of atherosclerosis means that perioperative myocardial infarction (PMI) is of significant concern to anesthesiologists. Perioperative revascularization (if indicated medically), beta blockade (in high risk patients) and statin therapy are therapeutic modalities that are currently employed to reduce PMI. Statins not only lower low density lipoprotein levels but, via their actions on the isoprene pathway, exhibit pleiotropic effects. Statins stabilize vulnerable plaque, predominantly via their anti-inflammatory effects, and improve the functioning of the endothelium in atherosclerosis. These effects appear to reduce the perioperative complications of atherosclerotic lesions. It is important to have an understanding of newer developments in the pathophysiology of atherosclerosis to be able to appreciate the mechanisms of action of statins. The focus has changed from identification of stenotic coronary lesions to the identification of vulnerable plaque. This review is divided into 2 parts. The first part focuses on the pathophysiology of atherosclerosis. The second part will be published in a later issue and will discuss the pharmacology of statins and the mechanisms whereby they may reduce the incidence of PMI.

## Introduction

Prevention of perioperative myocardial infarction (PMI) in non-cardiac surgery commences preoperatively with evaluation of the risks of the individual patient for perioperative infarction. The algorithm proposed by the American Heart Association and the American College of Cardiologists (AHA/ACC) is based on currently available evidence and represents the approach used by most anesthesiologists at present. Using clinical predictors, exercise tolerance and the perceived surgical risk, this algorithm evaluates the risk of PMI and suggests the best approach to minimise the risk.<sup>1</sup>

One of the consequences of the AHA/ACC algorithm is that patients may be presented for coronary angiography and coronary revascularization before non-cardiac surgery. Such intervention is of doubtful benefit.<sup>2,6</sup> Less invasive interventions such as percutaneous coronary angioplasty, and/or coronary stenting, initially promised better perioperative outcomes. Subsequent experience has taught that a high risk of perioperative thrombosis and occlusion exists if non-cardiac surgery is performed within the first 35 days, and probably longer, after coronary stent placement.<sup>7,10</sup> In addition, the concomitant prescription of antiplatelet drugs has to be considered in the patient with a coronary stent.<sup>11</sup> The approach proposed by the AHA/ACC, albeit a valuable clinically orientated evaluation tool, does not necessarily reduce perioperative cardiac complications after non-cardiac surgery.<sup>9</sup>

It has been suggested that improved drug therapy may significantly reduce the incidence of PMI.<sup>2</sup> There is a growing body of evidence that beta adrenoreceptor blockade,<sup>12-19;19-22;22-25</sup> can reduce PMI and other perioperative cardiac complications by up to 85%<sup>26</sup> in patients at high risk,<sup>17,27,28</sup> especially when tight heart rate control is achieved.<sup>29-33</sup> Statins are also potentially useful in

the prevention of PMI. This review focuses on the pathophysiological reasons that statins are potentially useful in preventing PMI.<sup>11</sup> To understand how statins work, it is important to review the initiation of, development, and pathophysiology of the complications of atherosclerosis. The aspects that are covered include the following:

Part 1: Pathophysiology of atherosclerosis.

- Development and maturation of atherosclerotic plaques.
- Pathophysiology of complications that occur due to atherosclerotic plaques in the non-surgical population.
- The changing perspective of cardiology: from critical stenosis to inflammatory process and vulnerable plaque.
- Pathophysiology of PMI.

Part 2: Mechanisms of action of the statins (Will be published in a later issue).

## PART 1

### Pathophysiology of atherosclerosis

#### *Initiation, development and maturation of atherosclerotic plaques*

##### *Initiation of atherosclerosis*

The exact mechanisms whereby atherosclerosis is initiated are currently not known.<sup>34, 35</sup> The response to injury hypothesis suggests that various factors can damage the endothelium. Diabetes, hypertension, smoking, ischemia and hyperhomocystinaemia are all considered factors that can do this. Traditionally, high levels of low density lipoprotein (LDL) are considered to be the factor initiating atherosclerosis,<sup>36</sup> and yet over half of all deaths from atherosclerosis occur in patients

without overt hyperlipidemia. Other non-traditional risk factors, such as inflammation, are now considered to play an aggravating role.<sup>35</sup> After starting an atherogenic diet heavy in cholesterol and saturated fats, one of the first occurrences is the accumulation of low density lipoprotein (LDL) particles in the intima of arteries.<sup>34</sup> These lipoproteins undergo various chemical alterations that include oxidation and glycation. More extensive non-enzymatic glycation occurs in diabetics with sustained hyperglycemia and may be responsible for the acceleration of atherosclerosis.<sup>35, 38</sup> Oxidised and glycated LDL are powerful pro-inflammatory agents that contribute to the subsequent cellular events causing atherosclerotic lesion development.

#### *Leukocyte recruitment and accumulation*

Normally, arterial endothelial cells have a low affinity for, and usually resist adhesion of circulating leucocytes. Even in inflamed tissue, most entry of leucocytes into tissue occurs in post capillary venules, and not in arteries.<sup>34, 35, 38</sup> Oxidised and glycated LDL induces local chemo-attractant cytokine production. Both locally expressed, and circulating cytokines, such as tumour necrosis factor alpha and interleukin-1, stimulate the expression of certain immunoglobulins such as vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1).<sup>34, 35, 38</sup> (Endothelial cells normally express E-selectin, P-selectin, ICAM-1 and VCAM. ICAM and VCAM are only expressed when the endothelium is stimulated by cytokines and endotoxin. It is likely that E-selectin, an adhesion molecule that normally plays a role in the rolling of leucocytes on the endothelium, plays a lesser role in the initiation of atherosclerosis).<sup>34, 37, 39, 40</sup> The increased expression of cell adhesion molecules induces not only the predominant attachment of monocytes, but also T lymphocytes to arterial endothelial cells.<sup>34, 35, 38</sup>

Once the leukocytes are adherent to the endothelium, they require a signal to enter the intima. Inflammatory process induce release of chemo-attractant cytokines, one of the most important of these is monocyte chemoattractant protein 1 (MCP-1). MCP-1 is not only a chemotactic agent, but also facilitates leukocyte diapedesis between endothelial cell junctions so that they enter the intima.<sup>34, 35, 38</sup>

#### *Foam cell and fatty streak formation*

On entering the intima, monocytes transform into macrophages. The macrophages, now located in the intima, encounter stimuli such as macrophage colony stimulating factor (M-CSF) which activates them and also causes them to replicate.<sup>34, 38</sup> The consequences of activation are that the macrophages increase their expression of surface scavenger receptors.<sup>34, 38</sup> These scavenger receptors are different to the normal LDL receptors on the surface of most cells. These receptors are ordinarily subject to negative feedback inhibition when the cell has enough cholesterol from LDL for its metabolic needs.<sup>34</sup> Scavenger receptors, by employing receptor-mediated endocytosis, facilitate the excessive uptake of lipoprotein and modified lipoprotein particles present in the intima. The lipoproteins are both stored and modified (oxidised) within the macrophages in an attempt to detoxify the intima<sup>38</sup> of the blood vessels. Many of these macrophages leave the arterial wall in an attempt to clear lipid from the developing lesion.<sup>38</sup> Macrophage-monocytes that have ingested much LDL have a characteristic vacuolated appearance

on microscopy and are termed "foam cells" or lipid laden macrophages.<sup>34, 38</sup> A collection of foam cells is termed a *fatty streak*, being the beginning of an atherosclerotic plaque. Although the endothelium overlying such a fatty streak may be raised, it is anatomically intact. Nonetheless, this intact endothelium is dysfunctional.

The *macrophage foam cells* present in the early atherosclerotic plaque do not only accumulate lipids; these cells are metabolically active.<sup>36</sup> M-CSF and cytokines, such as tumour necrosis factor alpha and interleukin-1, stimulate augmented production of a host of macrophage enzymes, growth factors and small molecules such as oxygen radicals.<sup>38</sup> Macrophages therefore act as a rich source of factors that:

- Promote *cell proliferation and migration* (e.g. smooth muscle cell mitogens, oxygen radicals),
- Break down local tissue barriers (e.g. oxygen radicals, matrix metalloproteinases),
- Activate inflammatory gene expression via the nuclear factor kappa B transcriptional control system,<sup>39</sup>
- Destroy nitric oxide radicals, decreasing the effect of NO and,
- Provide an additional source of cytokines.<sup>38</sup>

#### *Smooth muscle cell migration, proliferation and production of the fibrous cap*

As the plaque matures, smooth muscle cell mitogens cause smooth muscle cells in the tunica media to slowly migrate into, and proliferate in, the arterial intima. Damage to the dense extracellular matrix, caused by matrix metalloproteinases (see next paragraph), facilitates migration of smooth muscle cells from the media into the intima. These smooth muscle cells exhibit a less mature phenotype than the quiescent smooth muscle cells in the tunica media and are also metabolically more active.<sup>38</sup> Smooth muscle cells normally produce extracellular matrix macromolecules such as collagen, proteoglycans and elastin, for normal maintenance of the arterial wall. Cytokines and growth factors, such as platelet-derived growth factors and transforming growth factor beta, potentially induce smooth muscle cells to express generous amounts of extracellular matrix proteins. This is responsible for the production of the fibrous cap that overlies more mature atherosclerotic plaques. Eventually the majority of the volume of the plaque may consist of collagen.

The fibrous cap is not a static structure. It exhibits significant metabolic activity and can undergo considerable remodelling.<sup>41</sup> The accumulation of the fibrous cap depends on a balance between biosynthesis of the extracellular matrix molecules counteracted by the breakdown by proteolytic enzymes. These proteolytic enzymes are matrix metalloproteinases (MMPs), produced by foam cells in response to inflammatory stimuli such as TNF alpha, IL-1, oxidised LDL and activated T lymphocytes. The latter has a ubiquitous presence in inflamed plaque. MMPs can degrade virtually all components of the extracellular matrix.<sup>35, 35, 42</sup> Inhibitors of MMPs known as tissue inhibitors of metalloproteinases (TIMPs), can both inhibit the catabolism of the extracellular matrix macromolecules and also delay the deployment of smooth muscle cells in the developing lesion.<sup>34</sup> It is noteworthy that atherosclerotic plaques that suffer rupture of the fibrous cap have fewer smooth muscle cells i.e. fewer cells synthesize the elements giving the fibrous cap its strength.<sup>41</sup>

### *The mature plaque*

Inflammatory cytokines cause the death, predominantly by apoptosis, of smooth muscle and foam cells.<sup>34</sup> Necrosis of smooth muscle and foam cells results in the development of a necrotic lipid core in the plaque.<sup>38</sup> A mature plaque therefore consists of a fibrous capsule, and a relatively acellular collagen rich connective tissue that surrounds an area of soft lipid rich necrotic cellular material. The initial fatty streak evolves into a fibrofatty lesion containing both *atherosis* (soft atheromatous gruel containing necrotic cells and lipids) and *sclerosis* (the presence of fibrous tissue).<sup>34, 38</sup>

### **Endothelial function in atherosclerosis**

Endothelial dysfunction is a term frequently used to refer to the loss of endothelium dependent vasodilatation as a result of lower levels of nitric oxide in the vessel wall.<sup>43, 44</sup> It also refers to several other pathological endothelial states, namely abnormal anticoagulant functions, impaired modulation of vascular growth and dys-regulation of vascular remodeling.<sup>43</sup>

The normal endothelial cell surface is antithrombotic and expresses significant amounts of thrombomodulin, tissue plasminogen activator and nitric oxide. Only small amounts of factor 7, von Willebrand factor and plasminogen activator inhibitor-1 are released.<sup>45</sup> Thrombomodulin binds circulating thrombin and activates the anticoagulant, protein C. Endothelial dysfunction has been repeatedly shown to be a consequence of hypercholesterolemia, even in the absence of atherosclerotic plaque formation.<sup>46, 47, 48</sup> Thrombomodulin expression is down regulated.<sup>49</sup> The ligand for CD40 (CD40L) is a membrane glycoprotein homologue of TNF alpha that is expressed on the surface of activated T lymphocytes and other cells implicated in atherosclerosis.<sup>49, 50</sup> Increased LDL-cholesterol results in more intimal inflammation with activation of T lymphocytes and greater expression of the CD40L.<sup>49, 50</sup> A number of inflammatory mediators such as the CD40 ligand, tumor necrosis factor alpha and interferon gamma, cause macrophages, smooth muscle and endothelial cells to over-express tissue factor.<sup>49</sup> Furthermore, in atherosclerosis, there is an increased level of von Willebrand factor and the ratio of tissue plasminogen activator to plasminogen activator inhibitor-1 favors the latter.<sup>49</sup>

The normal endothelium expresses nitric oxide synthetase (eNOS) in small arteries in response to a number of stimuli, especially shear stress.<sup>51</sup> Oxidized LDL reduces expression of nitric oxide because of reduced stability of nitric oxide m-RNA.<sup>49, 52</sup> Lack of NO contributes to impaired endothelium dependent vasodilatation, platelet aggregation, enhanced leukocyte aggregation and raised blood pressure.<sup>43, 53</sup> Reduced levels of NO may prevent vaso-dilatation and actually lead to vasoconstriction and organ ischemia, for example myocardial ischemia in the presence of eccentric plaques.<sup>51</sup> High levels of LDL also reduce nitric oxide expression in platelets, increasing the platelet aggregation response to various stimuli.<sup>49</sup> Nitric oxide is not only a vasodilatory molecule, but also has important antiplatelet, anti-inflammatory and atheroprotective effects.<sup>48, 49</sup> Nitric oxide's atheroprotective effects stem from its inhibition of leukocyte adhesion to endothelial cells through suppression of endothelial cell expression of adhesion molecules, vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1.<sup>48</sup> In summary, the endothelium in atherosclerosis favors a prothrombotic,

vasoconstrictory environment, promoting a greater chance of occlusive thrombus formation if a plaque does indeed rupture.<sup>49</sup>

### **Mechanisms whereby complications occur**

Atherosclerosis is a chronic disease, the majority of atherosclerotic plaques being clinically silent for decades.<sup>34, 38</sup> Furthermore, not all atherosclerotic plaques have the same composition or anatomical morphology (e.g. eccentric and concentric lesions) and generate problems via different mechanisms. Growth of plaques is not always linear but at intervals, exhibits sudden progression.<sup>34, 38</sup> For anesthesiologists, myocardial infarction represents the most common acute complication of atherosclerosis, with strokes occurring less frequently, but due to similar pathology. The two main causes of myocardial infarction in general (non-surgical, non perioperative period) are plaque rupture and ulceration.<sup>11</sup>

*Fibrous cap fissuring or rupture* is responsible for 60 to 75% of all (non-surgical and anesthesia related) myocardial infarctions.<sup>34, 38</sup> The necrotic lipid core typically contains a large amount of macrophage produced tissue factor; exposure of factor VII to blood will result in thrombus formation. The thrombi that form are of differing sizes.<sup>35, 48</sup> It is known that increased levels of inflammation result in greater amounts of tissue factor being produced by plaque macrophages and a larger clot can be formed.<sup>35</sup> Inflammation also stimulates macrophages to produce plasminogen activator inhibitor 1 (PAI-1) which inhibits fibrinolysis.

The consequences of fibrous cap rupture are variable. Some, but not all fibrous cap disruptions, give rise to immediate catastrophe. If the thrombus is occlusive and little or no collateral blood supply exists, myocardial ischemia and infarction will occur. If the thrombus is non-occlusive, temporary narrowing of the vessel can result in an episode of unstable angina. Should this thrombus be resolved by fibrinolysis or be washed away and embolise peripherally, the patient may experience a period of unstable angina that eventually passes. If coronary angiography is performed after clot resolution, it may reveal little or no stenosis in the area of the coronary responsible for the infarction or symptoms. Distal emboli may cause myocardial infarction by lodging in, and occluding, smaller vessels distal to the primary lesion.<sup>37</sup>

*Small fissures and ruptures* of the fibrous cap of an atherosclerotic plaque are quite common and are often unaccompanied by significant clot formation. Very frequently, these occurrences are clinically silent, yet these small repeated disruptions stimulate a healing fibrotic response in the plaque.<sup>34</sup> Large percentages (typically more than 70% by volume) of such plaques are eventually made up of fibrous tissue.<sup>42</sup> This fibrous tissue can encroach on the lumen of the vessel resulting in significant coronary artery stenosis that is typically associated with a pattern of "stable" exercise induced angina. The large quantity of fibrous tissue means that these fibrous atherosclerotic plaques do not readily rupture.<sup>42</sup> The relatively rapid development of fibrosis in response to injury is one explanation why atherosclerotic plaques have long periods of quiescence punctuated by periods of sudden evolution.<sup>34, 42</sup>

Inflammation with increased expression of matrix metallo-proteinases does not only result in plaque rupture, but

can also damage the proteins anchoring endothelial cells to the subendothelial matrix. The consequence of this is that endothelial cells, or parts of them, break loose from the underlying sub-cellular matrix, exposing an extremely thrombogenic surface. The thrombus that frequently forms on top of the ulcerated area can lead to unstable angina or infarction. About 20 to 40% of acute myocardial infarctions in the general population occur via this mechanism. Increases in coagulability associated with LDL levels, smoking and hyperglycemia, aggravate thrombus formation on top of endothelial ulcerations.<sup>11</sup>

***What factors are associated with plaque susceptibility to rupture, or what factors define a “vulnerable plaque”?***<sup>4, 55</sup>

The fibrous cap proteins provide dynamic strength and ability to withstand shear forces applied to the plaque. If the fibrous cap is thick, the “plaque” is relatively stable and will not tend to rupture. Should the fibrous cap be thin, less than 65 to 150 microns, the plaque may become vulnerable to rupture.<sup>11, 42</sup> Atherosclerotic plaques, with a large necrotic lipid core, comprising more than 40% of the total area of the lesion, are also highly susceptible to rupture.<sup>11, 42</sup> The thin fibrous cap and large necrotic lipid core, imply that the wall stress in the fibrous cap is high. Indeed, research has demonstrated that vulnerable plaques rupture at the point of maximal wall stress.<sup>42, 56</sup> Such increases in wall stress can occur with increases in blood pressure.<sup>42</sup> Repeated increases in stress can also be responsible for fatigue of the fibrous cap. Lowering of the heart rate and reduction of coronary blood flow velocity, may reduce the risk of rupture associated with tissue fatigue.<sup>42</sup>

***How do plaques develop characteristics that make them vulnerable to rupture?***

The thin cap and large lipid core are usually the result of active inflammatory processes in the atherosclerotic plaque.<sup>57, 58</sup> These inflammatory processes and some of their consequences include:

- In the presence of persistently high levels of LDL, the lipid core grows and the inflammatory response progressively develops inside the lesion.
- Both local and systemic inflammatory processes promote infiltration of macrophage-monocytes and inflammatory cells, predominantly T-lymphocytes, into the lesion. It is indeed a hallmark of vulnerable plaques that a considerable amount of inflammatory cells are present.<sup>58</sup>
- The T lymphocyte and other cytokines also activate macrophage foam cells to express inflammatory mediators, growth factors

and matrix metalloproteinases. Matrix metalloproteinases catabolise collagen and elastin within the fibrous cap.

- Furthermore, T lymphocytes produce gamma interferon that inhibits collagen production by smooth muscle cells.

Thus, the extracellular matrix that confers biomechanical strength to the plaque's fibrous cap is under a two pronged attack, decreased synthesis and increased degradation, in the presence of inflammation. This double assault results in a thinning and weakening of the fibrous cap and subendothelial matrix.

***The changing focus in identification of coronary lesions: from critical stenosis to inflamed vulnerable plaque***

Until relatively recently, cardiologists (and anesthesiologists) have focused on angiographically detectable high grade stenoses as the critical issue in coronary artery disease. In other words, it has been thought that the greater the stenosis, the greater the risk of a clinical event such as myocardial infarction or unstable angina pectoris.<sup>59</sup> There is indeed some older evidence supporting this approach in the coronary artery surgery (CASS) study.<sup>42, 60, 61</sup>

The focus on the stenotic lesion detectable by angiography is changing. The reasons are that most plaques grow outward from the lumen of the vessel wall (termed abluminal extension) and do not cause coronary obstruction. In addition, compensatory enlargement of the coronary artery occurs where plaques are forming.<sup>62</sup> These two aforementioned pathophysiological entities make the artery appear tortuous. Despite the absence of coronary artery stenosis, significant plaques may still exist. Only after the size of a plaque approaches half of the luminal area does it start to encroach into the lumen and become visible angiographically.<sup>59</sup> Coronary angiography therefore underestimates the incidence and severity of clinically silent vulnerable plaques. These vulnerable plaques usually far outnumber the severely obstructive lesions and can be very prone to rupture with consequent myocardial infarction.<sup>42, 59</sup> In fact, most plaques that underlie a myocardial infarction cause less than 70% stenosis of a coronary artery.<sup>40</sup> An acute plaque rupture is also more likely to lead to an acute coronary syndrome as there are less collaterals than would be the case in chronic high grade obstructive lesions.<sup>42</sup> Libby,<sup>59</sup> a prolific writer on the subject of unstable plaque, stated as long ago as 1995 that “The presence of severe stenoses may merely serve as a marker for the presence of angiographically modest or even in-apparent plaques actually more prone to precipitate myocardial infarctions”.

**Table :** PMI and underlying coronary artery stenosis.

PMI % total	Cause of PMI	Coronary stenosis	Time of death	Therapeutic options
54%	Stress	High grade	Days 1 -3	Beta Blockers (Without ISA)
46%	Plaque rupture	Absent or low grade	Evenly spread over perioerative period	Statins ?

Adapted from references 51 and 70.



The focus on inflammation and the vulnerable plaque is an important aspect of current thinking about the pathophysiology of atherosclerosis. It appears that inflammation plays a central role at all stages of atherosclerosis and makes plaque more vulnerable to rupture.<sup>59</sup>

Inflammation is not only a local event occurring in the adventitia of atherosclerotic arteries, but is frequently a reflection of a global process.<sup>63</sup> Systemic inflammatory processes are so important in the atherosclerotic process that increased systemic markers of inflammation indeed predict the severity of atherosclerosis and future coronary events. Ultra-sensitive C reactive protein (Us-CRP) is not only a biomarker of inflammation but is also a pro-inflammatory and pro-thrombotic molecule that advances the atherosclerotic process and causes plaque destabilisation. Us-CRP levels have been shown to be an extremely useful predictor of overall levels of inflammation, plaque stability and future cardiac events even in adults without known coronary artery disease.<sup>64, 67</sup> Ridker and colleagues have shown that Us-CRP levels of 1.0 mg/L, 1.0 mg/L to 3.0 mg/L and 3.0 mg/L represent low, medium and high cardiovascular risk respectively. Large epidemiological studies have also found increased risk of vascular events in subjects with elevated basal levels of other inflammatory mediators such as the cytokines IL-6 and TNF-alpha.<sup>68-70</sup> Furthermore, CRP and other pro-inflammatory cytokines are produced by visceral fat. This explains why patients with centripetal obesity are at increased risk of developing vulnerable plaque and myocardial infarctions, and why waist-hip ratio is an important predictor of future cardiac atherosclerotic events.

That inflammation is important, is further emphasised by the observation that there is a higher incidence of atherosclerosis in patients with chronic infection due to dental caries, periodontal disease, prostatitis and bronchitis.<sup>35</sup> Evidence of infection with chlamydia pneumoniae, helicobacter pylori, hepatitis A and herpes simplex virus 1 are independent markers of the extent and severity of coronary artery disease.<sup>35, 71, 72</sup> These infections are associated with endothelial dysfunction, increased CRP levels (a biomarker of systemic inflammation) and the release of greater amounts of pro-inflammatory mediators by vascular endothelial cells, smooth muscle cells and macrophage foam cells in atherosclerotic lesions.<sup>35, 71</sup> The aforementioned observations tie in very well with research indicating that toll-like receptors are expressed on the surface of endothelial cells, and macrophages, in atherosclerotic plaques.<sup>72, 73</sup> The cells that expressed the toll-like receptor respond to bacterial and viral pathogens by activating nuclear factor kappa beta. Activation of nuclear factor kappa beta stimulates a wide array of inflammatory genes.<sup>72, 73</sup> These bacteria and viruses most likely do not initiate atherosclerosis, but probably stimulate inflammation, thereby activating existing atherosclerotic lesions.<sup>72-74</sup>

Increased levels of inflammatory markers such as CRP, interleukin 1 and interleukin 6 relate to in-hospital and short-term prognosis after acute coronary syndromes.<sup>35, 75, 76</sup> Furthermore, subsequent event free survival after an acute coronary syndrome is related to achieving and maintaining CRP levels of less than 2 mg/L.<sup>77, 78</sup> One way of identifying the presence and extent of vulnerable plaque is by using intravascular ultrasound to visualize large lipid pools and plaques that have a high wall stress and might

be prone to rupture. Other imaging techniques (MRI, CT scanning) are also currently being employed to identify the extent of the plaque load in individual patients.

The result of this improved understanding of the pathophysiology of atherosclerosis, is that identification of patients at risk for plaque rupture represents a major focus in cardiology, and will probably become of increasing importance to perioperative medicine. Whether Us-CRP, measurement of which can be performed from a sample of peripheral venous blood, is indeed a predictor of perioperative events, is not as yet known with certainty, but represents an area for future research.<sup>79</sup>

### Pathophysiology of perioperative myocardial infarction

If physicians wish to prevent PMI, it is important to understand the pathophysiology of PMI. The pathophysiology of PMI is poorly investigated but appears to be similar to myocardial infarctions not related to anesthesia and surgery.<sup>11</sup> Evaluation of complementary data from 2 sources reveals that two predominant pathophysiological causes are responsible for these patterns:<sup>61, 80</sup>

1. Early PMI, the highest incidence occurring immediately postoperatively, is associated with the presence of high grade coronary lesions. Ischemia and infarction associated with this type of lesion are due to perioperative stress (most often during laryngoscopy and intubation, or extubation) causing tachycardia and hypertension that results in myocardial ischemia. Approximately half of all PMI's occur due to stress induced events in patients with high grade stenoses. In this regard, the liberal use of preoperative beta blockers, especially in intermediate and high risk patients, may prove useful to reduce PMI in anesthesia practice, although there is currently significant controversy about this issue in the literature.<sup>81, 82</sup>
2. The other 50% of PMI's are caused by vulnerable coronary plaque rupture or endothelial desquamation with subsequent thrombosis and occlusion of coronary arteries. This type of PMI is spread out over the perioperative period. They can even occur in the late postoperative period as long as 3 to 4 days after surgery. Priebe suggests that the transformation from a chronic stable atherosclerotic lesion to a vulnerable plaque can indeed be an acute event.<sup>11</sup> In this regard, Poldermans and Schouten hypothesize that the perioperative inflammatory response with release of inflammatory cytokines<sup>83-85</sup> TNF alpha and IL-1 and IL-6 may make plaques more vulnerable and explain late PMI. Furthermore, postoperative hypercoagulability ("vulnerable blood")<sup>11, 54, 59</sup> may contribute to PMI.

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