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REVIEW ARTICLE

The pathophysiology of peri-operative myocardial infarction

B. M. Biccard[1] and R. N. Rodseth[2]

1 Principal Specialist, 2 Specialist, Inkosi Albert Luthuli Central Hospital, Department of Anaesthetics, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, South Africa

Summary

It is generally believed that plaque rupture and myocardial oxygen supply-demand imbalance contribute approximately equally to the burden of peri-operative myocardial infarction. This review critically analyses data of post-mortem, pre-operative coronary angiography, troponin surveillance, other pre-operative non-invasive investigations, and peri-operative haemodynamic predictors of myocardial ischaemia and/or myocardial infarction. The current evidence suggests that myocardial oxygen supply-demand imbalance predominates in the early postoperative period. It is likely that flow stagnation and thrombus formation is an important pathway in the development of a peri-operative myocardial infarction, in addition to the more commonly recognised role of peri-operative tachycardia. Research and therapeutic interventions should be focused on the prediction and therapy of flow stagnation and thrombus formation. Plaque rupture appears to be a more random event, distributed over the entire peri-operative admission.

Correspondence to: Bruce M. Biccard
E-mail: biccardb@ukzn.ac.za
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Patients with or at risk of cardiac disease have a 3.9% (95% CI 3.3–4.6%) risk of suffering a major peri-operative cardiac event [1]. A peri-operative myocardial infarction has an associated in-hospital mortality of 15–25% [1] and an increased risk of subsequent cardiovascular death or myocardial infarction [2].

Despite this important prognostic information, there are a number of controversial and poorly understood issues surrounding peri-operative myocardial infarction. There is well established evidence that an increasing heart rate is associated with peri-operative myocardial ischaemia and myocardial infarction [3]. However, substantial evidence suggests that hypotension, hypoperfusion and coagulation are important precipitants of early peri-operative myocardial ischaemia and infarction. Understanding peri-operative myocardial infarction pathophysiology is important in addressing appropriate peri-operative therapies, which in turn have important public health implications.

Presentation of peri-operative myocardial infarction

Time of presentation

Since the introduction of troponin surveillance, most peri-operative myocardial infarctions are identified within the first postoperative day [4], compared with identification between 48 and 72 h when creatine phosphokinase was used. The day of presentation [5–7] of a peri-operative myocardial infarction is shown in Fig. 1.

Although the majority of peri-operative myocardial infarctions present within the first 4 days of surgery, and nearly 90% by 7 days, the range of presentation is throughout the entire hospital admission [7]. After the seventh postoperative day approximately 1% of peri-operative myocardial infarctions present per day [5–7].

Pattern of presentation of troponin elevation

A study of aortic surgical patients identified three patterns of troponin elevation [8]. The first pattern was characterised

by a rapid rise in troponins peaking at a mean (SD) of 37 (22) h postoperatively. The second pattern displayed a delayed mean (SD) peak in troponins at 74 (39) h following 54 (35) h of troponin elevation above the upper reference limit [8]. Finally, the third pattern of troponin elevation was characterised by troponins above the reference limit without a late peak. This pattern was termed 'myocardial damage' [8]. It was proposed by the authors that coronary plaque rupture was consistent with early peri-operative myocardial infarction due to the rapidity of troponin change, while a sustained myocardial oxygen supply-demand imbalance in the postoperative period was consistent with delayed myocardial infarction [8]. This conclusion, however, is probably incorrect. Indeed, the authors of this paper comment that the study was not designed to determine the pathophysiology of a peri-operative myocardial infarction [8]. The reasons why their conclusion, is probably incorrect are discussed in the following section.

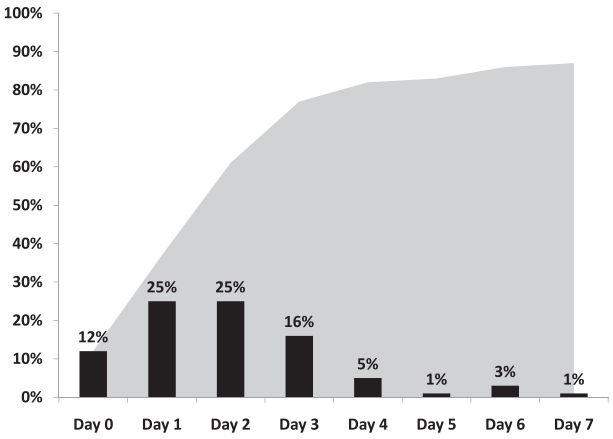

Figure 1 Cumulative (grey) and proportional (black) presentation per day of peri-operative myocardial infarction. Data from references [5–7].

The pathophysiology of peri-operative myocardial infarction

The pathophysiology of peri-operative myocardial infarction is both complex and poorly understood, especially when compared with myocardial infarction in medical patients. In the latter, approximately 70% of fatal myocardial infarctions are associated with ruptured coronary plaques [9]. The remaining 30% of patients have unruptured plaques but some features known to be associated with plaque vulnerability including erosions and calcified nodules [9]. The result is that non-stenotic lesions dominate in medical myocardial infarctions [9].

In addition to troponin surveillance, our understanding of peri-operative myocardial infarction is based on a further five separate investigative approaches. These include post-mortem studies, pre-operative angiographic studies, pre-operative tests of inducible myocardial ischaemia, peri-operative Holter studies and peri-operative haemodynamic studies.

Post-mortem studies

Post-mortem studies have shown firstly, that in patients who die, the peri-operative cardiac event appears to be approximately evenly distributed between myocardial oxygen supply-demand imbalance and plaque rupture [6, 10]. It is possible however, that plaque rupture may contribute proportionally less to fatal peri-operative myocardial infarction than myocardial supply-demand imbalance, as evidence of plaque rupture was found in only 7% of patients [10]. A further 45% of the patients had features of intra-plaque haemorrhage, which does not strictly signify plaque rupture in these patients [10]. The second study had documented plaque rupture in 46% of the patients [6].

The second important characteristic identified in the post-mortem studies was that there was no evidence of plaque rupture in 83% of patients who died within the first three postoperative days and 77% of patients who died within the first 4 days [6]. Thus although plaque rupture and myocardial oxygen supply-demand balance may be evenly distributed in fatal peri-operative myocardial infarctions, myocardial oxygen-supply demand imbalance predominates in the early (first 3–4 days) postoperative period.

Thirdly, patients with associated plaque rupture were evenly distributed over 17 postoperative days [6]. The presentation of plaque rupture therefore appears to be randomly distributed throughout the postoperative period, while myocardial oxygen supply-demand imbalance predominates in the early postoperative period.

The fourth important finding of the post-mortem cases is that fatal peri-operative myocardial infarction occurs against the background of established coronary artery disease. Significant coronary stenoses were identified in 50% of the patients [10], and significant three vessel coronary disease in 44% of the patients [6]. Coronary thrombus was present most often at these sites of significant coronary stenosis (89%) representing 31% of the total number of cases. The remaining coronary thrombus was identified in the absence of plaque rupture [6]. Importantly, total coronary occlusion with thrombus was only identified in 56% of the patients with evidence of thrombus, and only 19% of all the patients that died [6]. These findings suggest that low-flow states secondary to coronary stenoses are probably more important than

plaque rupture with total coronary occlusion in the peri-operative period.

Pre-operative coronary angiography

A matched case control study of pre-operative coronary angiographic findings in vascular surgical patients found that the only independent predictor of mortality was the number of lesions with > 30% stenosis [11]. Whether this was the only true independent predictor of fatal myocardial infarction was questioned, however, because of the probable overlap with a number of coronary features. The strongest univariate predictors were collaterals beyond a total occlusion and the number of significant stenoses > 50% ($p < 0.001$) in the patients who suffered myocardial infarction or death [11]. This study further supports the notion that established coronary artery disease with a degree of obstruction to flow is important in the pathophysiology of peri-operative myocardial infarction, and that the presence of collaterals does not necessary protect from fatal myocardial infarction. Indeed, 81% of the fatal cases had chronic total coronary occlusion, while only 29% of the nonfatal controls had a chronic total coronary occlusion [11].

Pre-operative tests of inducible myocardial ischaemia

The importance of significant coronary stenoses is evident when one examines the performance of pre-operative special investigations. The tests with the lowest negative likelihood ratios (of approximately 0.2) for major adverse cardiac events are pre-operative dynamic tests of inducible myocardial ischaemia (Table 1). This suggests that the patients in whom no inducible ischaemia is elicited are unlikely to have peri-operative cardiac complications.

While the presence of established coronary artery disease appears to be an important risk factor for peri-operative myocardial infarction, the site of infarction is not necessarily dependent on the site of the significant stenosis. Peri-operative myocardial infarction correlated with the site of inducible ischaemia in 81% of patients, although 56% of patients had evidence of infarction in other coronary territories [22].

While a negative test result for inducible myocardial ischaemia is clinically accurate (likelihood ratio 0.2), a positive test result is not as accurate at predicting an adverse outcome (positive likelihood ratios of approximately 4), suggesting that once a patient has coronary pathology associated with an increased risk of peri-operative

Table 1 The performance of clinical risk indices and pre-operative investigations in predicting peri-operative major adverse cardiac complications. Values are number (95% CI).

Pre-operative test	Sensitivity; %	Specificity; %	PPV; %	NPV; %	LR; neg	LR; pos
Goldman's class IV*	53	99	56	99	0.48	65
Detsky class III						10.6[a]
Lee's RCRI 0 or 1 point	89	62	5	97	0.24	1.46
Inability to walk 4 blocks and climb 2 flights of stairs[b]†	71	47	20	90	0.61	1.34
< 2 flights of stairs[d]‡	33[b]	48[d]	0.6	99	0.63	1.58
Radionuclide ventriculography	50 (32–69)	91 (87–96)	32[e]§	93[e]§	0.6[e]§ 0.81–0.96[a]	4.1[e]§ 1.41–6.24[a]
Ambulatory ECG	52 (21–84)[e]§ 68[f]	70 (57–83)[e]§ 66[f]	8.9[e]§	95[e]§	0.8[e]§	1.5[e]§
Exercise ECG	74 (60–88)[e]§ 69[f]	69 (60–78)[e]§ 73[f]	10[e]§	98[e]§	0.34[e]§ 0.17–0.89[a]	2.54[e]§ 1.3–2.56[a]
Dipyridamole stress echo	74 (53–94)[e]§ 85[f]	86 (80–93)[e]§ 80[f]	17[e]§	99[e]§	0.28[e]§ 0.19[f]	4.95[e]§ 4.25[f]
Myocardial perfusion scintigraphy	83 (77–89)[e]§	49 (41–57)[e]§	11[e]§ 4–20[g]¶	97[e]§ 95–100[g]¶	0.37[e]§ 0.44[h]	1.61[e]§ 1.83[h]
Dobutamine stress echo	85 (74–97)[e]§ 90[f]	70 (62–79)[e]§ 30[f]	15[e]§ 7–25[g]	99[e]§ 93–100[g]	0.24[e]§ 0.23[h]	3.75[e]§ 4.09[h]
CPET[c,i,j]*	85	71.7	8	99	0.21	4.64

CPET, cardiopulmonary exercise testing; ECG, electrocardiogaphy; echo, echocardiography; LR, likelihood ratio (neg/pos, negative/positive); NPV, negative predictive value; PPV, positive predictive value; RCRI, Revised Cardiac Risk Index.
*In-hospital cardiovascular mortality.
†All complications during hospitalisation.
‡All cause mortality.
§30-day cardiovascular mortality or myocardial infarction.
¶Vascular surgical patients.
a [12], b [13], c [14], d [15], e [16], f [17], g [18], h [19], i [20], j [21].

myocardial infarction, a number of other factors are necessary for these lesions to result in an adverse outcome, following myocardial oxygen supply-demand imbalance in the early postoperative period, or plaque rupture throughout the hospital admission.

Peri-operative Holter studies

Studies of peri-operative myocardial ischaemia have shown that in vascular surgical patients, 20% of all patients have postoperative ST depression [23]. The latter is nearly 40 times more common than ST elevation on peri-operative Holter monitoring [24], occurring in under 3% of patients [24]. Again, this finding suggests that total coronary occlusion is less common than myocardial oxygen supply-demand imbalances in the peri-operative period. Myocardial oxygen supply-demand imbalance may result from the presence of significant stenoses [6, 10, 11, 22], in the presence of partial occlusion from plaque rupture [6], or low-flow states associated with thrombosis [6] or increased postoperative myocardial oxygen demand [25].

It is important to note that ST depression precedes troponin elevation in 83% of vascular surgical patients by approximately 18 h [24]. Ninety-seven percent of vascular surgical patients present with ST depression within the first 72 h of surgery, suggesting the predominance of oxygen supply-demand imbalance as opposed to complete coronary occlusion at this time [24].

Peri-operative haemodynamic studies

Postoperative myocardial ischaemia is more common than pre-and intra-operative myocardial ischaemia [3, 24, 26, 27]. The duration of postoperative myocardial ischaemia generally exceeds that of pre- or intra-operative myocardial ischaemia [3, 28]. Myocardial ischaemia associated with postoperative myocardial infarction is usually prolonged (> 30 min [29] to > 120 min [30, 31]). Many studies report an association between an increase in heart rate and/or a relative tachycardia and postoperative myocardial ischaemia [28, 29, 32, 33].

Although a left ventricular mass > 270 g has been shown to be an independent predictor of coronary plaque rupture within the following 6 months in patients with stable coronary artery disease [34], peri-operative hypertension is uncommonly associated with peri-operative myocardial infarction. Hypotension is more commonly associated with peri-operative adverse cardiac outcomes [35–37] than hypertension, and has been associated with a composite adverse peri-operative outcome [38].

Prolonged intra-operative hypotension (defined as > 20 mmHg reduction in mean arterial pressure for > 60 min) results in a significant increase in cardiac deaths, myocardial infarctions and cardiac arrests [35, 36], even after adjusting for a history of cardiac disease [36]. It is notable that when the duration of hypotension is considered, a larger reduction in mean arterial pressure does not appear to add significantly more risk of ischaemic complications [36]. Ignoring the duration of hypotension or a short time epoch (such as 5 min) in the definition of intra-operative hypotension may result in hypotension's not being identified as an independent predictor of adverse cardiac events [38, 39]. The severity of the nadir in blood pressure may then become important [37]. These studies suggest that the duration of hypotension is an important determinant of an adverse cardiac outcome.

More recently, when adverse cardiac outcomes have controlled for duration of surgery and/or blood administration, the univariate association of hypotension and/or tachycardia with cardiac adverse events has been not found to be an independent predictor [37, 40]. Certainly, the administration of blood may conceal the importance of both hypotension and tachycardia. The importance of hypotension in some patients may be one of the reasons why the rate-pressure product has not been found to be a consistent predictor of peri-operative myocardial ischaemia.

Summary of the pathophysiology of peri-operative myocardial infarction

Based on these studies, the following pathophysiological processes are probably responsible for peri-operative myocardial infarction. Peri-operative myocardial infarction is most likely to occur in patients with significant coronary artery stenoses. In the first three to four postoperative days, patients probably have a relative flow-mediated hypoperfusion that precedes myocardial infarction (more commonly at the site of significant stenoses (> 80%), than following non-occlusive thrombus after coronary plaque rupture). Hypoperfusion may be aggravated by hypotension or intracoronary thrombosis secondary to hypercoagulability and inflammation, possibly further aggravated by an increased myocardial oxygen demand associated with surgery, pain and sympathetic stimulation. This process precedes troponin elevation in 80% of patients by approximately 18 h. Even a rapid rise in troponins within the first two postoperative days, as shown by Le Manach and colleagues [8] following aortic surgery, is more likely to represent a severe oxygen supply-demand imbalance (possibly aggravated by thrombus formation) than plaque rupture. Peri-operative myocardial infarctions following plaque rupture are more likely to resemble medical myocardial infarctions and are evenly distributed in the postoperative period. Our understanding of the pathophysiology of fatal peri-operative myocardial infarction is summarised in Table 2.

Table 2 The pathophysiology of fatal peri-operative myocardial infarction. Values are proportion or mean (SD).

Characteristic of myocardial infarction	Supply-demand imbalance	Plaque rupture
Significant coronary stenosis	≥ 95% of all myocardial infarctions	
Incidence	45–56%	44–55%
Multivessel coronary stenoses	86%	92%
Presence of intraluminal thrombus	0–7%	52–66%
Postoperative day of presentation	4.4 (4.8)	7.8 (4.4)

Data from references [6, 10, 22].

The physics of coronary blood flow and implications for peri-operative myocardial infarction

The question must be asked as to whether flow disturbances due to coronary artery plaque-induced stenosis result in coronary artery thrombus, independently from plaque rupture or fissure? Examining the physics of flow associated with coronary artery disease allows one to evaluate the role that perfusion pressure, velocity and coagulation may play in peri-operative myocardial infarction.

The classic model describing the factors predisposing to thrombus formation encompasses abnormalities of flow, endothelium and coagulation, also known as Virchow's triad [41]. In the early postoperative period (0–5 days) these three factors are ideally grouped together to create optimal conditions for the formation an intracoronary thrombosis without plaque rupture. We propose the hypothesis that intracoronary thrombus formation may occur commonly without plaque rupture in the early postoperative period, with the two key events being post-stenotic blood flow stasis induced by hypotension, and platelet activation.

Flow abnormalities

Stationary fluid in a pipe exerts a force or pressure on the vessel's walls. This force, applied at 90 degrees to the vessel wall, is described as a normal mechanical stress. When the fluid moves through the pipe the force is applied tangentially or parallel to the face of the vessel and is termed a shear stress. Factors affecting the magnitude of the shear stress are the viscosity of the blood (η) and shear rate. Shear rate is the change in blood velocity (v_1–v_2) over a certain distance (h) [42]. Thus:

$$\text{Shear stress} = \eta \times (v_1 - v_2)/h$$

In a lumen with a fixed diameter the shear rate becomes directly proportional to the velocity gradient (v_1–v_2).

Where a fluid such as blood interacts with a solid boundary such as a vessel wall, its velocity is rapidly reduced as it approaches the wall, finally reaching zero against the vessel wall. This thin layer of fluid exhibiting velocity reduction is known as the boundary layer. If there is an intrusion into the lumen of the vessel, as occurs with a coronary plaque, the fluid in the boundary layer will follow the shape of the stenosis, generating new flow patterns or streamlines until the speed of flow in the boundary layer reaches zero. At this point the streamline detaches from the wall in a phenomenon known as boundary layer separation. As the fluid separates it forms an area of low pressure behind the stenosis with regions of reverse flow or recirculation [43].

The Reynolds number describes the flow of the fluid in relation to a surface. With turbulent flow, which occurs at a Reynolds number > 2000, more energy is imparted to the boundary layer and flow separation occurs at a later point. This high energy turbulent flow disrupts the more organised recirculation patterns seen with laminar flow. Reynolds number:

$$\text{Re} = \rho\ (\text{density}) \times V(\text{mean fluid velocity}) \times D\ (\text{tube diameter})/\eta\ (\text{dynamic viscosity})$$

Blood velocity may be derived from the Poiseuille equation [42]:

$$Q = \pi r^4 (P_1 - P_2)/8\,\eta l$$

Where r = radius of the blood vessel, $P_1 - P_2$ = pressure gradient in the vessel and l = length of vessel. Once the volume flow has been determined, the average velocity can be obtained by dividing Q by the cross-sectional area of the vessel (πr^2). This then results in average velocity:

$$\text{Average velocity} = r^2 (P_1 - P_2)/8\,\eta l$$

If density, diameter, vessel length and viscosity remain fixed in a particular vessel then the Reynolds number with its resultant blood flow patterns, as well as the shear stress, is directly proportional to blood flow velocity; and blood flow velocity is directly proportional to pressure gradient. Thus blood flow patterns and shear stress can be shown to be directly proportional to the pressure gradient.

While both tachycardia and hypertension may precipitate peri-operative plaque rupture by increasing coronary blood velocity, and a relative tachycardia has been associated with early postoperative myocardial ischaemia [3, 44], the post-mortem studies reviewed previously [6, 10] do not support the expected plaque rupture following an increase in shear stress associated with increased blood velocity. Indeed, the pathophysiology suggests that relative hypotension and a reduction in blood velocity

associated with a fall in the pressure gradient across the coronary artery are probably important co-existing physiological aberrations necessary to convert peri-operative myocardial ischaemia into peri-operative myocardial infarction.

Periods of sustained hypotension result in reductions in blood velocity, with resultant low energy laminar flow patterns in the post-stenotic regions around the coronary plaque. These patterns, described as regions of recirculation and flow reversal, result in flow stagnation [45, 46] and provide conditions conducive to thrombus formation [47–50]. Although, surgical post-mortem studies have shown few thrombi in patients without evidence of plaque rupture, there is evidence to suggest that thrombolysis occurs in a number of patients before death [51]. In vascular surgical patients, a positive correlation between myocardial ischaemia and a marker of fibrinolysis has been shown as early as 15 min to 4 h postoperatively ($r = 0.59–0.78$, $p < 0.002$) [52]. In patients without myocardial ischaemia it appears that markers of fibrinolysis may be evident later, possibly after 24 h postoperatively [53].

When multiple sequential stenoses are present, significant pressure reductions may occur, with flow separation taking place at lower blood velocities than with single stenoses, creating a larger degree of stasis [54]. This is consistent with the only independent pre-operative coronary angiography predictor of peri-operative mortality [11]. The post-mortem studies [6, 10] are also suggestive of this feature, with three-vessel coronary artery disease reported in 60% of fatal myocardial infarctions [10] and multivessel coronary artery disease in 88% of fatal myocardial infarctions [6] (Fig. 2a).

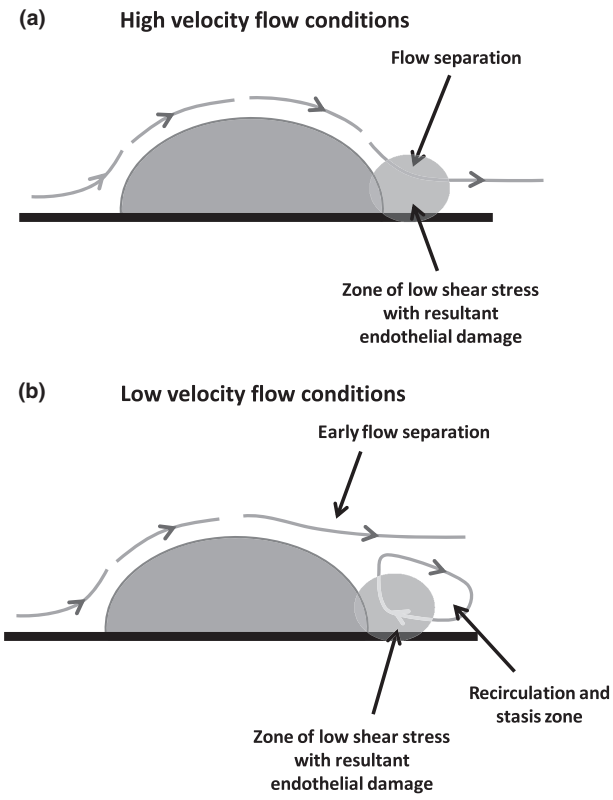

Figure 2 (a) High velocity blood flow results in streamlines demonstrating late flow separation. At the point of flow separation the endothelial wall experiences a low shear stress with resultant endothelial dysfunction. (b) Low velocity blood flow conditions result in the formation of streamlines that demonstrate earlier flow separation. This earlier separation forms zones of recirculation and stasis, which now overlap with the zone of endothelial damage, predisposing to thrombosis formation. Redrawn from [47, 48, 59].

Platelet activation

High shear stress conditions (> 70 dynes.cm^{-2} (> 7 Pa)) result in platelet activation [55]. Activation is mediated either by direct mechanical force, or by von Willebrand factor interaction [47]. As a result of inter-platelet interaction, as platelet counts increase so platelet activation increases exponentially [56]. Peak shear rates are experienced at the apex of the stenosis where deposition of platelets and fibrin occur and it is likely that peri-operative tachycardia may prime platelets for thrombus formation.

Platelets that do not adhere in this high shear region undergo activation or become primed to react more easily on subsequent exposure to platelet agonists. On entering the post-stenotic recirculation zone they are exposed to a low shear stress milieu, allowing cellular interaction and thrombus formation to take place [47]. In postoperative vascular patients, platelets have been shown to be more prone to activation [53]. Furthermore, by following patients having major vascular surgery, a relationship between platelet activation and postoperative elevations of troponin-I has been shown [57]. In the recirculation region, red blood cells, which are normally found centrally in the blood flow stream, undergo clumping and interaction with both platelets and neutrophils, further contributing to thrombus formation [58].

Endothelial substrate

Local endothelial wall shear stress is crucial in maintaining normal endothelial function and integrity. This stress is normally in the region of 30 dynes.cm^{-2} (3 Pa). The effect of low (< 6 dynes.cm^{-2} (< 0.6 Pa)) and oscillatory sheer stress on endothelial function is discussed in detail in an excellent review article by Chatzizisis et al. [59]. In these regions the endothelium undergoes an up-regulation of pro-inflammatory cytokines increasing the expression of adhesion molecules (vascular adhesion molecule (V-CAM), intercellular adhesion molecule (I-CAM) and

E-selectin) whilst down-regulating the production of endothelial nitric oxide synthetase (eNOS), prostacyclin and tissue plasminogen activator (t-PA) – factors all resulting in increased plaque thrombogenicity.

Endothelium that underlies a region of flow separation is exposed to low shear stress with subsequent prothrombotic changes. When the pressure gradient drops and laminar flow patterns predominate, damaged activated endothelium is available to interact with activated platelets in a region of blood stagnation (Fig. 2b).

Summary

In postoperative vascular surgical patients with damaged coronary endothelium and luminal stenosis, the already primed platelet is now ideally poised to become fully activated. When provided with zones of flow stagnation resulting from periods of sustained hypotension, the ideal conditions for the development of intracoronary thrombosis are present in the early postoperative period.

Conclusion

While the role of tachycardia in peri-operative myocardial ischaemia is relatively well established, critical examination of various modalities of investigation of peri-operative myocardial ischaemia and infarction suggest that flow stagnation and thrombus formation are probably critical factors contributing to myocardial infarction in the early postoperative period.

Confirmation of this hypothesis is essential, as it would focus further research in patients at risk of peri-operative myocardial ischaemia on peri-operative haemodynamic determinants of coronary hypoperfusion and the need for more aggressive antiplatelet and anticoagulation management in the peri-operative period.

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