Involvement of leucocytes and leukotrienes in ischaemic dysfunction of the coronary microcirculation

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KEY WORDS: Myocardial ischaemia, myocardial infarction, granulocyte, coronary blood flow.

Recent evidence suggests that leucocytes may exert an important influence on microvessel flow during pathophysiologic conditions. This is particularly true in the case of coronary occlusive disorders. Diminution of coronary perfusion pressure favours trapping of the large, stiff leucocytes in capillaries. Perhaps more importantly, ischaemic changes in the endothelial lining of microvessels promote early sequestration of leucocytes within capillaries of ischaemic regions during underperfusion and, to a much greater degree, during reperfusion. If these trapped leucocytes are activated by the ischaemic environment, the mechanical plugging of microvessels can be significantly complicated by leucocyte release of a variety of materials affecting the function of blood vessels and myocytes.

Leukotrienes are a potent group of inflammatory mediators released by activated leucocytes. A subgroup, the peptidoleukotrienes (C₄, D₄, and E₄), has a profound vasoconstrictor influence on coronary microvessels. Members of this group can also cause platelet aggregation. Agents that block peptidoleukotriene synthesis, such as nafazatrom, have been reported to diminish the adverse effects of myocardial ischaemia. However, these agents often have non-specific actions that blur the interpretation of their anti-ischaemic efficacy. Our laboratory has made a number of observations that cast doubt—or at least stimulate further inquiry—on the role of peptidoleukotrienes on promotion of sustained microvessel constriction in ischaemic coronary beds. Most importantly, we found that continuous intracoronary administration of leukotriene C₄ or D₄ led initially to marked diminution of coronary flow and myocardial contractility. However, this was soon followed by a complete, dose-independent escape from these effects even though leukotrienes continued to be infused at a constant rate. The cause of this escape is unclear, but it may involve a specific product released when leukotrienes interact with platelets. In a second series of experiments, we found that the coronary constrictor efficacy of bolus leukotrienes (and also the stable thromboxane A₂ analogue, U46619) was markedly reduced by concomitant myocardial ischaemia. Constrictor responses were rapidly restored with reperfusion, suggesting a transient metabolic blockade of constrictor responsiveness during myocardial ischaemia. Nevertheless, these data indicate that leukotrienes may not act simply as agents that exaggerate underperfusion due to proximal coronary occlusion. Finally, we have measured the leukotriene immunoreactivity in coronary venous blood exiting from beds made ischaemic (and dysfunctional) by partial occlusion of epicardial arteries. Although the occlusion was sufficient to cause release of lactate and other metabolic markers of ischaemia, we were unable to find measurable rises in release of any of the leukotrienes after occlusions lasting 3 h and reperfusions lasting up to 1 h.

We conclude that a substantial body of evidence suggests that leucocytes play a significant role in the pathogenesis of ischaemic and post-reperfusion myocardial damage. In part, this may relate to their actions on microvessel performance, although further investigation is needed to elucidate the mechanisms involved. Our studies do not confirm the potential importance of leukotrienes in myocardial ischaemia. Instead, they indicate that microvessels somehow show a rapid escape from the...
constrictor influence of certain leukotrienes. In addition, microvessels exhibit little response to the leukotrienes when these beds are experiencing ischaemia. Lastly, we were unable to detect a significant rise in leukotrienes released in coronary venous effluent from markedly ischaemic myocardial regions.

Further studies are needed to establish a definite pathologic role for leukotrienes during the course of myocardial ischaemia due to epicardial coronary occlusion.

Introduction

Coronary flow in normal hearts is dominated by autoregulatory influences on the microcirculation, i.e., local release and removal of adenosine, modulated by tonic release of vasoactive materials from endothelium and local nerve endings. Under abnormal conditions microcirculatory function can be disturbed by altered elements in blood, the vessel wall, or surrounding tissues. Recently, increasing attention has focused on ways that leucocytes, particularly polymorphonuclear leucocytes (PMN), could cause microcirculatory damage in myocardium rendered ischaemic by large-vessel coronary occlusion. Highly sensitive to foreign stimuli and capable of a variety of potent cytotoxic or transforming responses, leucocytes are likely mediators of inflammatory change in the microcirculation. The purpose of this article is to review leucocyte-mediated mechanisms of injury to microcirculatory function during and after ischaemia with emphasis on the possible role of leukotrienes, a family of arachidonate-derived leucocyte products with substantial capacity to affect microcirculatory flow.

Leucocytes and the coronary microcirculation

A number of clinical disorders are thought to involve leucocyte participation in microcirculatory injury: adult respiratory distress syndrome, septic states, and severe systemic allergy (anaphylaxis). Leucocytes may also participate in coronary microcirculatory damage after myocardial ischaemia initiated by epicardial coronary occlusion. Prior depletion of circulating PMN or pharmacologic suppression of leucocyte function has been shown to reduce the extent of post-ischaemic myocardial contractile dysfunction and necrosis in experimental models of acute coronary occlusion1-4. These results suggest a leucocyte-mediated amplification or extension of ischaemic injury. The mechanisms involved here have not been fully defined. However, they are likely to entail three key steps: 1) leucocyte entrapment in microvessels, with possible migration into adjacent tissues; 2) leucocyte activation to release a variety of potentially toxic or vessel-altering materials; and 3) action of leucocyte products on neighbouring vessels, blood constituents (platelets or plasma) and myocytes (Fig. 1).

Leucocyte entrapment will occur in any situation involving reduced tissue perfusion15,6. Circulating PMN are stiff, bulky cells that ordinarily traverse capillaries with greater difficulty than do other blood elements. Thus, when arteriolar pressure is reduced due to proximal coronary artery occlusion, PMN will be trapped in microvessels by a reduction in the

![Figure 1](image-url) Key steps in polymorphonuclear leucocyte (PMN) amplification of ischaemic tissue injury. Initially, lodgment of PMN in the microvessels of ischaemic regions (left) occurs due to low propelling pressures, leucocyte bulk, and, most importantly, enhanced adhesiveness of PMN and the endothelial cells lining the microvessels. Inflammatory mediators present in ischaemic tissue then activate lodged PMN, causing them to release cytotoxic substances (centre). Finally, superoxide anions (O2·-), leukotrienes (LT) and lytic enzymes from PMN act to extend damage in nearby microvessels and myocytes (right).
Adherence of polymorphonuclear leukocytes (PMN) to endothelial cells is stimulated by a variety of substances, including polypeptides, leukotriene B4 (LTB4), cytokines (such as interleukin-1) and thrombin. These stimuli transform the membranes of each cell type to make them more adherent. Recent evidence suggests that this change is mediated by intracellular release of platelet-activating factor (PAF), a ubiquitous membrane phospholipid (P-LIPID) that can also come from stimulated platelets (PLT). Enhanced PMN adhesiveness may occur due to the expression of specific (MO-1) receptors and adhesive proteins from the complement cascade (C3b).

Propelling pressure gradient and possibly by a diminution in microvessel diameter due to decreased distending pressure. Physically mediated deposition of PMN can be augmented by increased stickiness of the endothelial cells that line blood vessels and of the PMN themselves. Squeezed into relatively narrow myocardial capillaries, the large PMN develop a broad area of contact between themselves and the subjacent capillary endothelium. Surface membrane properties that determine cell stickiness are known to change in response to mediators of inflammation (Fig. 2). For example, the ubiquitous phospholipid, platelet-activating factor (PAF), greatly enhances PMN adherence to endothelial cells. PAF and other inflammatory mediators promoting leukocyte adherence are probably released in the course of myocardial ischaemia. Thromboxane A2, and other platelet products issuing from a proximal coronary arterial lesion will have a similar influence. Accumulation of PMN will also occur in response to ischaemia-initiated release of chemotactic factors such as leukotriene B4 (LTB4) and the cytokines, interleukin-1 and tumour necrosis factor. Physical influences and cell-to-cell signalling induced by ischaemia or thrombosis collectively cause a substantial increase in PMN present in ischaemic tissues, particularly after reperfusion, when PMN delivery to the injured tissues is greatly enhanced.

Deposition of PMN in microvessels due to a brief reduction in pressure gradient is likely to be a reversible process. Restoration of pressures could dislodge these cells unless there are associated changes in membrane adhesiveness. However, the local ischaemia engendered by capillary occlusion may well lead to permanent lodgment with the passage of time and enhancement of PMN adherence to endothelium by inflammatory mechanisms. Engler et al. have shown that PMN lodgment is a major factor in the 'no reflow' phenomenon, the failure of capillary reperfusion (and consequent death of metabolically active tissue elements) after restoration of arterial pressure in tissue rendered ischaemic by prolonged occlusion of a nutrient artery.

Once PMN are lodged in capillaries, they are particularly subject to 'activation', a process that rapidly transforms these leucocytes from relatively inert transients to potent agents of tissue dysfunction and destruction. An important feature of host defences against bacterial invasion, activation of PMN results in abundant production of oxygen-derived free radicals (superoxide anions and hydroxyl radicals), highly reactive species that chemically alter and
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Damage cell membranes and other structures subject to oxidative injury. PMN activation also leads to degranulation and release of a variety of lytic enzymes, such as neutrophil elastase, that dismantle macromolecules and destroy cells. Activated PMN release leukotrienes, potent vasoactive lipid mediators, which will be discussed subsequently. The changes in physical properties of PMN described earlier, i.e., increased adhesiveness and stiffness, are part of activation and reflect concomitant cytoskeletal alterations.

Several inflammatory mediators lead to chemoattraction and, in somewhat higher concentrations, activation of PMN. LTB₄, a particularly potent chemoattractant and cell activator, plays a key role in PMN recruitment at sites of inflammation. Other effective activators include components of the complement cascade (reflecting the role of PMN in host defence), and PAF. These agents act by promoting intracellular hydrolysis of phosphatidylinositol and thereby increasing PMN cytoplasmic calcium levels. The specific mechanisms by which ischaemia initiates attraction and activation of PMN have not yet been defined. It is likely that multiple inflammatory mediators are eventually involved since the recruitment process is autocatalytic.

The oxygen-derived free radicals, lytic enzymes, and leukotrienes produced by activated PMN are likely to figure significantly in mediating the initial stages of ischaemic injury. Some of the benefit of PMN inhibition or removal may be due to attenuation of microcirculatory blockade caused by physical obstruction, release of vasoconstrictors, or oxidation of the endogenous vasodilator, endothelium-derived relaxing factor. This possibility is suggested by a diminution of postischaemic rise in coronary vascular resistance with PMN removal. However, suppressed release of materials directly cytotoxic to myocytes (oxygen-derived free radicals or neutrophil elastase) may be the predominant source of benefit. Although the nature of leucocyte participation may not yet be fully delineated, it seems likely that activated PMN are significant mediators of myocardial ischaemic injury. The therapeutic implications of these findings remain somewhat uncertain. Naturally, any restriction of inflammatory responses or PMN function could have a significant adverse impact on long-term function of intact individuals. Nevertheless, it seems possible that some mode of suppression of PMN influence during or after ischaemic insult may ultimately prove to have practical therapeutic utility.

Leukotrienes as mediators of coronary microcirculatory dysfunction

Leukotrienes are potentially important agents of leucocyte influence on coronary microvessels. They are a family of chemically related substances produced by the actions of a specific enzyme, 5-lipoxygenase, on a ubiquitous membrane constituent, arachidonic acid. The resulting unstable epoxide intermediate, leukotriene A₄, may be enzymatically hydrolysed to form LTB₄ or combined with glutathione to form peptide leukotrienes C₄, D₄, and E₄. When all three amino-acid residues of glutathione remain attached, the product is leukotriene C₄ (LTC₄). Removal of a single amino-acid residue converts LTC₄ to leukotriene D₄ (LTD₄), and removal of a second amino-acid residue forms leukotriene E₄ (LTE₄). Leukotrienes are not appreciably stored in cells. Rather, they are synthesized de novo by activated leucocytes, which uniquely possess the requisite enzyme systems. Leukotriene synthetic capability is shared by PMN, basophils, eosinophils, and lymphocytes. Leukotriene synthesis in solid tissues, such as the lung, is likely to be due to the action of resident macrophages or mast cells. The metabolic fate of leukotrienes has not been fully delineated. In well-perfused tissues, peptide leukotrienes are rapidly transported to the liver, where they are further metabolized and excreted in the bile.

The physiologic actions of the leukotrienes fall into two categories. As mentioned above, LTB₄ is a powerful attractant and activator of leucocytes. However, LTB₄ has little influence on other cell types. In contrast, the peptide leukotrienes fail to activate leucocytes but do have many other effects, principally mediated by their ability to stimulate smooth muscle contraction. Details of their actions vary somewhat with species. In general, LTC₄ and LTD₄ share a potent capacity to constrict the smooth muscle of bronchial pathways, small intestine, and many vascular beds. Minute amounts of LTC₄ can lead to profound
bronchospasm. The peptide leukotrienes also promote local formation of oedema.

Peptide leukotrienes have substantial cardiac actions. Administration of LTC₄ or LTD₄ to ex vivo hearts causes severe, prolonged coronary constriction, marked decrement in myocardial contractility, and ventricular arrhythmia. When given in vivo as intracoronary bolus doses, peptide leukotrienes lead to transient, dose-related decrements in local coronary blood flow and contractile performance. These observations suggest that locally released peptide leukotrienes could significantly complicate episodes of epicardial coronary occlusion. Ischaemic myocardium might experience PMN accumulation and leukotriene release. The depressant actions of peptide leukotrienes on myocardial perfusion and contractility might exacerbate the effects of the initial ischaemic insult, leading to enhanced myocardial necrosis and left ventricular dysfunction. Blockade of leukotriene synthesis or efficacy would then seem a logical therapeutic approach to prevent this sequence of events.

The hypothesized adverse effect of peptide leukotrienes just described implies that: 1) these lipid mediators have a sustained adverse effect when presented over a prolonged period, 2) they are capable of inducing coronary constriction in the presence of an independent, pre-existing ischaemic condition, and 3) they are synthesized in significant amounts within ischaemic regions. To explore the potential role of peptide leukotriene release during mechanically-initiated myocardial ischaemia, we performed studies that addressed each of these issues.

**Critique of the actions of peptide leukotrienes**

Results in our laboratory have indicated that sustained infusions of LTD₄ uniformly result in 'escape', complete reversal of coronary flow decrement and associated reduction in myocardial contractility. This is also true for several other microvessel constrictor agents: the stable thromboxane A₂ analogue U-46619, arginine vasopressin, and PAF.

We examined the escape response using intracoronary infusion of LTD₄ (0.3–3.0 μg min⁻¹) for 7–24 min into the left anterior descending (LAD) coronary arteries of pentobarbital-anaesthetized, open-chested domestic pigs (Fig. 3). Animals were instrumented

![Figure 3](image-url)
with an electromagnetic flowmeter cuff proximal to the infusion site as well as epicardial piezoelectric crystal pairs within the LAD perfusion territory to assess regional shortening. Initially, there was a sharp decrease in coronary flow (by 25–55%) along with a significant reduction in regional systolic shortening (54–92%). In 35 of 40 pigs, local coronary flow and systolic shortening returned to preleukotriene baseline (escaped) within 2–4 min of starting the infusion and 1–2 min of frank ischaemia. This escape occurred independently of the rate of vasoconstrictor infusion and remained in effect even when the infusion persisted for as long as 24 min. The only abnormality observed during the escape period was a reduction in maximal hyperaemic coronary flow. Abrupt discontinuation of vasoconstrictor infusion during the escape phase did not result in any haemodynamic response; there was no evidence of overshoot due to sudden unmasking of compensatory vasodilator mechanisms. In the remaining five pigs, persistent leukotriene-induced constriction (without escape) was accompanied by severe myocardial ischaemia and death. Intracoronary infusion of arginine-vasopressin, 1 μg min⁻¹, in five other pigs produced initial constriction and subsequent escape similar to that observed with LTD₄. We considered the possibility that rapid induction of vasodilator metabolites via cyclo-oxygenase pathways might be responsible for escape. Neither cyclo-oxygenase blockade with indomethacin prior to LTD₄ infusion (Fig. 4) nor measurements of the stable metabolites of prostacyclin and thromboxane A₂ in the coronary circulation suggested involvement of cyclo-oxygenase products in the sequence of responses to LTD₄. Moreover, measurements of leukotriene levels (radioimmunoassay) in coronary venous effluent did not suggest that rapid degradation of infused material was a likely factor in escape.

To assess mechanisms of escape further, LTC₄, LTD₄, and arginine-vasopressin were injected as intracoronary boluses during intracoronary infusion of LTD₄. The constrictive effects of LTC₄ and LTD₄ were significantly attenuated during the escape phase, whereas vasopressin-induced coronary constriction was not altered. Hence, in situ, blood-perfused hearts of domestic pigs have the capacity to escape from the severe coronary constriction and myocardial depression induced by peptide leukotrienes and arginine-vasopressin. Spontaneous coronary escape from the influence of vasoconstrictors may play a useful role in maintaining myocardial perfusion under adverse circumstances. One mechanism of escape appears to be specific for leukotrienes and not mediated by vasodilator metabolites of arachidonic acid, such as prostacyclin. This mechanism of escape may result from the production of a specific antagonizing substance or rapid receptor desensitization. Further investigation showed that infused LTD₄ is transformed by platelets or leucocytes into a unique coronary vasodilator whose identity has not yet been determined. This vasodilator may be a principal mechanism of escape from leukotriene-induced coronary constriction.

If microvessel constriction due to release of peptide leukotrienes is a possible complicating factor in myocardial ischaemia, one might anticipate that these leukotrienes would retain their vasoconstrictor influence in microvessel beds subjected to substantial underperfusion due to epicardial coronary vessel narrowing. To assess the constrictor efficacy of arachidonate
metabolites in a coronary vascular bed experiencing ischaemia, open-chested domestic pigs were instrumented with an LAD coronary flowmeter, a catheter for intracoronary administration of test materials, and regional piezoelectric crystals, as described above. In addition, a snare was placed around the LAD distal to the flowmeter cuff and infusion line. Bolus doses of LTD₄ (1–10 µg) or the stable thromboxane A₂ analogue, U-46619 (1–10 µg) were evaluated before and during severe snare-induced coronary flow reduction, averaging 63 ± 2% of baseline. During ischaemic conditions we observed a marked, dose-independent attenuation of the coronary flow decrease consistently induced by the agonists before ischaemia (Fig. 5). With LTD₄ (10 µg) control coronary flow decrease of 35 ± 3 ml min⁻¹ (from 55 ± 4 ml min⁻¹ pretreatment baseline) was reduced (P < 0.001, n = 8 pigs) to 0.1 ± 0.1 (from 23 ± 3 ml min⁻¹ pre-LTD₄ baseline) during constriction caused by the snare. When retested 2–3 min after snare release (sufficient time for restoration of stable coronary flow), LTD₄ had completely regained its coronary constrictor capabilities. Similar results were observed with U-46619. Our data suggest that inflammatory mediators and possibly other potential microvessel constrictors may not add to coronary underperfusion imposed by a proximal occlusion. However, such constrictors may have an important influence on flow distribution after relief of proximal constriction. The mechanism by which coronary microvessels can attain dense and rapidly effective refractoriness to constrictors is not defined. The speed with which responsiveness recovers suggests physiologic antagonism by metabolically produced vasodilators or ischaemic paralysis of vascular smooth muscle rather than change in receptor availability. The mechanism inhibiting vasoconstrictor responsiveness during ischaemia may share some features with local vasodilator production during normal autoregulatory processes.

The experiments just described emphasize the ability of coronary microvessels to limit constrictor-induced ischaemic insult either through a rapid escape from constrictor effects or through refractoriness in the presence of mechanically induced underperfusion. These experiments were performed using a limited number of agonists, mostly arachidonate metabolites in a single species (domestic pigs). More recent results indicate that endothelin, a newly discovered peptide originally derived from endothelial cells, can produce coronary microvessel constriction and severe myocardial ischaemia with no evidence of escape. Nevertheless, our leukotriene data and the similar findings of Ertl et al. in dogs suggest some scepticism is needed when considering theories of ischaemic damage that postulate enhancement of ischaemic action by a sustained microvessel constrictor effect of peptide leukotrienes.

Involvement of leukotrienes in ischaemic myocardial damage requires that ischaemic insult leads to release of these materials in sufficient quantity and in an appropriate time-frame to influence the evolution of myocardial necrosis. Irreversible biochemical and morphologic changes characterizing tissue necrosis begin in the endocardial layers of the left ventricle 20–40 min after coronary occlusion. When occlusion persists, the
necrotic region expands toward the epicardial surface, reaching its full extent after 2-5 h. Thus, if leukotrienes participate in events leading to myocardial necrosis primarily through their action on vessels, they must attain levels sufficient to alter coronary vascular performance very soon after development of coronary occlusion. Previous studies have demonstrated enhanced arachidonic acid metabolism by ischaemic myocardium. Experimental data suggest increased myocardial release of both prostacyclin and thromboxane $A_2$ during ischaemia$^{29,30}$. The fact that arachidonic acid undergoes more rapid oxidative transformation via cyclo-oxygenase pathways favours the possibility that ischaemic myocardium will also exhibit more rapid oxidative transformation via 5-lipoxygenase pathways. Questions remain, however, whether increased amounts of arachidonic acid are available for 5-lipoxygenase metabolism in ischaemic myocardium and whether such enzyme systems are activated within ischaemic tissue.

We evaluated the possible role of leukotrienes in the evolution of myocardial necrosis by measuring levels of leukotrienes and other relevant substances in local coronary venous effluent during 3 h ischaemia (flow reduced 67-77%) and 1 h reperfusion (Fig. 6)$^{13}$. Six open-chested, pentobarbital-anaesthetized domestic pigs were instrumented with a flow probe around the LAD coronary artery and an inflatable occlusion cuff positioned 1-2 cm distal to the probe. A fine, non-occlusive polyethylene catheter was introduced into a portion of the coronary vein draining the arterial segment distal to the occlusion cuff. Appropriately placed piezoelectric crystals documented local ischaemia by showing contractile dysfunction during the period of occlusion. Coronary venous and paired arterial samples were analysed by radioimmunoassays detecting LTC$_4$/LTD$_4$ (LTC$_4$ immunoreactivity or LTC$_4$-ir)$^{20}$. LTD$_4$ and prostacyclin metabolite as well as standard methods for determining lactate. The assay for peptide leukotrienes (as LTC$_4$-ir) is able to detect changes in plasma level as small as 0.5 ng ml$^{-1}$. The sensitivity of this assay was confirmed by its ability to detect infused intracoronary LTD$_4$ sufficient to reduce unoccluded baseline flow by 50%: coronary venous LTC$_4$-ir rose from 0.9 ± 0.1 ng ml$^{-1}$ before LTD$_4$ to 7.0 ± 1.1 ng ml$^{-1}$ during LTD$_4$ infusion.

Our data showed an abrupt rise in coronary venous lactate during occlusion, further documenting the presence of significant myocardial ischaemia, with resolution on reperfusion. Coronary venous levels of prostacyclin metabolite also rose with ischaemia and increased even more during reperfusion. In contrast, coronary venous levels of LTC$_4$-ir and LTD$_4$ remained low during ischaemia and reperfusion. Arterial levels of all measured substances remained unchanged throughout the study.

The outpouring of prostacyclin metabolite, in agreement with other findings$^{29,30}$, suggests that arachidonic acid release and oxidative transformation to prostacyclin was enhanced in the ischaemic and early post-ischaemic myocardium of our pigs. The apparent lack of concomitant arachidonic acid transformation to leukotrienes may be explained by lack of access of substrate to appropriate enzyme systems, unfavourable
conditions for metabolism via 5-lipoxygenase pathways, or a lack of 5-lipoxygenase activity. Our studies do not discriminate among these possibilities. Lack of enzyme activity, however, is a particularly attractive hypothesis. Although sensitized cardiac tissues can release significant amounts of leukotriene-like material in response to antigenic challenge, perhaps because of the activity of mast cells, the 5-lipoxygenase system of cells present in newly underperfused myocardium may not respond similarly to ischaemic challenge. Leukotriene production is most characteristic of leucocytes, cells not present in abundance in the first few hours of myocardial ischaemia.

Our inability to detect a significant rise in peptide leukotriene levels with ischaemia does not seem related to insensitivity of assay methods. The large rise in local coronary venous LTC_4-ir during intracoronary LTD_4 infusion shows the capacity of our radioimmunoassay techniques to detect peptide leukotrienes when present in quantity sufficient to produce important coronary constriction. These same results also tend to exclude rapid degradation or sequestration of leukotrienes within coronary vessels as an explanation for lack of rise in LTC_4 with ischaemia.

Leucocytes and leukotrienes in acute myocardial ischaemia and infarction

Leucocytes may play an important role in the pathogenesis of myocardial ischaemia and infarction. Early adherence of leucocytes to coronary endothelium damaged by ischaemia and primed by inflammatory mediators may interfere with microcirculatory function by mechanically plugging vessels and by releasing oedema-promoting substances, vasoconstrictors such as 12-hydroxyeicosatetraenoic acid, or PAF. Leucocyte production of oxygen-dependent free radicals (e.g. superoxide anion), hydrogen peroxide, and other cytotoxic substances may augment myocyte damage and augment progression to necrosis as well as promote vasoconstriction by destroying endothelial-derived relaxing factor. Early leucocyte release of LTB_4 may be important in recruiting additional leucocytes, thereby increasing local superoxide anion generation. The absence of detectable levels of LTB_4 probably indicates that this potent chemotactic agent is highly localized within tissues and has minimal spillover into coronary venous blood. Sasaki et al. confirmed that recently infarcted rat hearts contained increased tissue levels of LTB_4—without associated change in LTC_4-ir. Nafazatrom, BW755C, and other inhibitors of 5-lipoxygenase have been reported to decrease infarct size. These drugs may interfere with PMN cytotoxicity by blocking synthesis of LTB_4 and, in the case of some of these agents, by direct inactivation of superoxide anion and other oxygen-dependent free radicals.

Although peptide leukotrienes might theoretically participate in the pathogenesis of an ischaemia-induced rise in coronary vascular resistance and in ischaemic myocardial necrosis from sustained coronary occlusion, our results do not substantiate this hypothesis. Infused peptide leukotrienes, mimicking an adverse situation that could occur during ischaemia, fail to produce sustained constrictive effects. Furthermore, leukotrienes and other arachidonic acid metabolites do not cause important constrictor actions in myocardium experiencing active ischaemia. Finally, levels of peptide leukotrienes generally associated with major constrictive effects do not appear promptly in coronary venous blood during and after myocardial ischaemia. Hence, blockade of synthesis or action of peptide leukotrienes may have little impact on coronary or myocardial function within 3 h of a coronary occlusion. By the time that sufficient leucocytes invade ischaemic myocardium to manufacture significant amounts of peptide leukotrienes, the myocardium may well have undergone irreversible necrotic changes.

Peptide leukotrienes may still have an important role in ischaemic events by promoting or sustaining thrombotic occlusion of epicardial coronary arteries. Current data appear to support an initiating rather than an exacerbating role for peptide leukotrienes in the pathogenesis of myocardial infarction.

This work was supported by the Uniformed Services University of the Health Sciences R08346. The opinions expressed here are those of the author. They do not reflect the views of the University or the Department of Defense. Experiments described here were conducted according to the principles set forth in Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council, DHEW Pub. No. (NIH) 74-23. The author is grateful to Drs Gordon Letts and Joshua Rokach, Merek-Frosst Inc.,
Dorval, Quebec, Canada, for performing radioimmunoassays and supplying synthetic leukotrienes. The author is also grateful to Mr John Czaja for his skilled technical assistance and to Mrs Joan McMillen for her help in manuscript preparation.

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