The Arachidonic Acid Metabolic Capacity of Canine Myocardium is Increased during Healing of Acute Myocardial Infarction

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SUMMARY. The relative capacity for metabolizing [14C]arachidonic acid into biologically active products was studied in microsomes prepared from both normal and infarcted regions of myocardium at three different times after circumflex coronary artery occlusion in the dog. At 3 days after infarction, when polymorphonuclear leukocytes were the predominant invading cell, the ability of infarcted left ventricle microsomes to produce arachidonic acid metabolites was greater than that of microsomes from normal areas of the same hearts. At 3 weeks after infarction, when macrophages were the predominant infiltrating cell and there was a proliferation of blood vessels and fibroblasts, there continued to be significant increases in the production of both prostacyclin (measured as 6-keto PGF$_{1\alpha}$) and thromboxane (measured as TxB$_2$). This enhanced production was still seen at 3 months after infarction at a time when histological examination of the tissue showed that it was still healing with both blood vessels and fibroblasts present. The production of 6-keto PGF$_{1\alpha}$ was 31.7 ± 4 picomoles per milligram protein per hour (pmol/mg per hr) in noninfarcted regions of left ventricle, whereas the production was significantly increased to 71.7 ± 15 at 3 days, 64.1 ± 10 at 3 weeks, and 67.2 ± 15 even at 3 months after infarction. The thromboxane synthetase activity rose significantly from 30.1 ± 5 pmol mg per hr in noninfarcted regions to 73.7 ± 18 at 3 days, 71.2 ± 5 at 3 weeks, and 92.4 ± 40 at 3 months. The enhanced ability to metabolize arachidonic acid may result from the inflammatory cell invasion or fibroblast activation which accompany healing of acute infarcts. (Circ Res 51: 743-750, 1982)

The heart can metabolize arachidonic acid into several prostaglandins (Minkes et al., 1973), the most prominent of which is prostacyclin (PG1$_2$) (Isakson et al., 1977; deDekere et al., 1977). The rate of prostaglandin synthesis in the heart is augmented by hormone stimulation (Needleman et al., 1975b), anoxia (Wenmalm et al., 1974; Needleman et al., 1975a), and ischemia (Block et al., 1974). Acute myocardial ischemia has recently been shown to be accompanied by an increase in the concentration of thromboxane (Tx) in the venous effluent, and this increase has been correlated with the frequency of acute ventricular dysrhythmias (Coker et al., 1981b). Pretreatment with aspirin (Coker et al., 1981a) or with the specific Tx synthetase inhibitor UK 37,248 (Coker et al., 1982) decreased both TxB$_2$ levels and the frequency of ventricular dysrhythmias, suggesting a causative relationship. Since platelets are known to accumulate in areas of ischemia (Laws et al., 1981), the acute Tx production could result from platelet aggregation within the ischemic myocardium during this acute postocclusion time period.

In addition to the malignant dysrhythmias associated with early ischemia, fatal dysrhythmias occur with increasing frequency during the subsequent days and weeks after the initial ischemic event. These late dysrhythmias occur when the myocardium is undergoing massive inflammatory cell invasion and fibroblast activation (Mallory et al., 1939; Fishbein et al., 1978). Little is known regarding arachidonic acid metabolism in the infarcted regions during this later time. The cells forming the fibrous scar at the site of an infarction are themselves capable of metabolizing arachidonic acid into active products that might influence the myocardium in which they reside. In this respect, the infarcted heart may be similar to the hydropnephrotic kidney which demonstrates an enhanced arachidonic acid metabolic capacity (Nishikawa et al., 1977) while it is undergoing interstitial edema and fibrosis (Nagle et al., 1973; Nagle and Bulger, 1978). We performed the present investigation to study arachidonic acid metabolism in the heart during evolving myocardial infarction and to assess the potential for enhanced synthesis of arachidonic acid metabolites in this tissue. Histological analysis of the tissue was also performed to determine whether the invading cell types present could be responsible for the increased synthesis of arachidonic acid metabolic products.

Methods

Infarction

Dogs of either sex were anesthetized with sodium thiopental (10 mg/kg iv) and anesthesia was maintained with halothane (0.5-1%). A transverse thoracotomy through the
Microsome Preparation

Microsomes were prepared from the myocardial tissue after removing the superficial epicardium along with any adherent tissue to avoid including pericardium in the preparation. When microsomes were not prepared immediately, the tissue was frozen in liquid nitrogen and stored at −70°C. The tissue was minced on ice, in three volumes of a sodium phosphate buffer (100 mM), pH 7.8, which contained 1% fatty acid poor bovine serum albumin (BSA-Calbiochem) to adsorb any released arachidonic acid and 10 mM EGTA to chelate Ca++ ions, thus inhibiting any calcium-dependent tissue phospholipases. The minced tissue was homogenized for 1 minute on ice in a Brinkman Polytron homogenizer. This homogenate was centrifuged for 10 minutes at 10,000 g at 4°C. The supernatant was removed and centrifuged for 1 hour at 100,000 g in a refrigerated Beckman ultracentrifuge. The surface of the resulting microsomal pellet was washed off with 100 mM sodium phosphate buffer (without EGTA or BSA). The pellet was resuspended on ice in a Dounce homogenizer by addition of 100 mM phosphate buffer to one-quarter of the original tissue sample volume. Aliquots of this microsomal suspension were taken for quantitation. When microsomes were not prepared immediately, an equal volume of ethylene glycol and 10 mM EGTA was added to the microsomal suspension to prevent aggregation. This mixture was frozen in liquid nitrogen and stored at −70°C. When inhibitors were used, they were added in a volume sufficient to give the desired final concentration. The reaction mixture was thawed and brought to room temperature when inhibitors were not used. The reaction mixture was rapidly mixed by vortexing and incubated for 1 hour at 37°C.

Extraction and Chromatography

At the end of the reaction interval, the incubations were acidified to pH 3.5 with formic acid (4 mM) and extracted three times with two volumes of ethyl acetate. The solvent was evaporated to dryness under a stream of nitrogen. The products were redisolved in a small volume of chloroform:methanol (2:1). Nonradioactive “cold” standards (6-keto PGF1α, PGE2, PGD2, TxB2, PGD3, PGE2—are courtesy of Upjohn, and arachidonic acid—NuChek) were added and the mixture applied to silica gel thin layer chromatography plates (POLYGRAM SIL G, Brinkman Instruments). The width of the bands at the origin was reduced by running the plates briefly, up to the origin (2 cm), three times, in chloroform:methanol (2:1). The plates were dried thoroughly and run in the “A9” solvent system (the organic phase resulting from the mixture of ethyl acetate, iso-octane, glacial acetic acid, water; vol/vol 110:50:20:100). The positions of the cold standards were determined with iodine vapor. Autoradiographic images were produced by “exposing” the plates to X-Omat XAR-5 film (Kodak) for 96 hours. Based on the migration of standards and on the autoradiographic image, product areas were defined and cut out for liquid scintillation quantitation (Research Products International-3a70 cocktail) with a Packard 460C liquid scintillation spectrometer. The entire plate was counted in order to calculate product formation as a percentage of the original substrate.

Statistics

The production rate is expressed as picomoles of product per milligram of microsomal protein per the 1 hour of incubation. Results are expressed as the mean ± SEM. Significance was calculated by Student’s t-test with a significance level of P < .05.

Histology

Transmural slices of myocardium from infarcted and control regions were fixed in 10% formalin, dehydrated in ethanol, embedded in paraffin and sectioned at 5 μm. Sections were stained with hematoxylin and eosin, Masson’s trichrome, or phosphotungstic acid-hematoxylin. In preparation for electron microscopy, tissue was minced into blocks (about 1 mm3), fixed in 3% glutaraldehyde in 0.1 M sodium cacodylate buffer, pH 7.4, postfixed in 1% osmium tetroxide, dehydrated in acetone, and embedded in Spurr’s low viscosity epoxy resin. Thin sections were prepared with a Sorval Porter-Blum ultramicrotome and diamond knife, stained with uranyl acetate and lead citrate, coated with carbon, and examined in a JEOL 100-C electron microscope at 60 keV.

Results

Histological Analysis of Infarct Healing

The normal histological appearance of canine myocardium is shown in Figure 1 (Normal). The tissue consists of a compact arrangement of myocytes, capillaries, and scattered interstitial fibroblasts. The fibroblasts have condensed nuclei and scant cytoplasm, reflecting a state of metabolic quiescence. Identical sections were seen in normal regions from infarcted hearts. The early or acute inflammatory phase of healing following ischemic necrosis is shown in Figure 1 (3...
Three days after coronary occlusion, the myocardial infarct is composed of degenerating necrotic myocytes and focally dense polymorphonuclear leukocyte (PMN) infiltrates. Platelet aggregates are present in the microvasculature of the infarct zone. The acute inflammatory phase subsides after reaching a peak at 3–5 days after infarction.

The disappearance of PMNs coincides with the onset of the chronic inflammatory and reparative phases of healing of myocardial infarcts. Interstitial fibroblasts and blood vessels at the periphery of the infarct proliferate markedly. By 3 weeks after coronary occlusion, the peripheral regions of large transmural infarcts and the bulk of smaller infarcts have been replaced by highly cellular and vascular granulation tissue [Fig. 1, (3 Week)]. At this stage, the fibroblasts have become densely packed and display basophilic (RNA-rich) cytoplasm and large vesicular nuclei with prominent nucleoli. These cytological features of fibroblasts reflect the intense metabolic activity required for collagen synthesis and export into the interstitium. The ongoing fibroplasia is supported by a rich network of newly formed blood vessels. At this stage, large infarcts still contain a core of necrotic cardiac muscle that was not resorbed during the acute inflammatory phase. At the junction of the ingrowing granulation tissue and the necrotic muscle, numerous macrophages create a resorption front and gradually remove the remaining debris. Thus, 3 weeks after coronary occlusion, the healing infarct contains three principal cell types—fibroblasts, vascular endothelium and macrophages—all with the histological appearance of a highly active metabolic state.

The ensuing weeks of infarct healing are characterized by complete replacement of necrotic muscle by granulation tissue and the maturation of granulation tissue into a fibrous scar. By 3 months, the granulation tissue is composed almost entirely of extracellular fibrous material, although residual fibroblasts and blood vessels still were present [Fig. 1 (3 month)]. The sparsely distributed fibroblasts do not appear metabolically active and are smaller and condensed compared to those at 3 weeks. Most, but not all, of the blood vessels have regressed. Macrophages and inflammatory cells are absent. Thus, at this stage, the infarct has begun the conversion into a nearly acellular and avascular mass of densely packed collagen.

Validation of Products

Products of arachidonic acid metabolism were identified by co-migration with known cold standards and by differential inhibition by selective enzyme inhibitors. Doses of inhibitors sufficient to cause complete inhibition were used. Dose-response curves verified the effectiveness of the doses used.

Figure 2 shows autoradiographs of AA metabolites and illustrates the differential effects of specific inhibitors. Autoradiographic bands of 14C-labeled products
coincided with the iodine-visualized bands. The first lane shows the products from the normal, noninfarcted left ventricle. The increase in products seen in the microsomes from a 3-week infarction is shown in the second lane. An unidentified nonpolar product is prominently increased in the infarcted tissue. Since, in the third lane, it is inhibited by incubation with the thromboxane synthetase inhibitor imidazole (5 mM), the nonpolar product may represent hydroxy heptadecatrienoic acid (HHT), the coproduct of thromboxane synthetase. The peak comigrating with TxB2 is similarly decreased by imidazole. The cyclooxygenase inhibitor indomethacin (14 μM, 5 μg/ml) inhibits the formation of all products, as shown in lane 4. 5,8,11,14-eicosatetraynoic acid (ETYA; 16 μM), which inhibits both cyclooxygenase and lipoxygenase, also inhibits the formation of all products shown in lane 5. No lipoxygenase products were seen in this microsomal preparation. The final lane of Figure 2 shows the boiled enzyme control for comparison.

**Microsomal Arachidonic Acid Metabolism**

Microsomes were prepared separately from samples of normal anterior left ventricle and infarcted lateral left ventricle. They were incubated with 24 μM 1-[^14]C]arachidonic acid for 1 hour at 37° after which the products were isolated by acid lipid extraction. The products were separated by thin layer chromatography and then quantified by cutting the zones comigrating with cold standards and counting the radioactivity in a liquid scintillation spectrometer. Production rates were calculated by converting the percent of total counts into an amount of product formed per milligram protein in the incubation per the 1 hour of incubation. Background levels of auto-oxidation were corrected for by running a boiled enzyme control and subtracting the background values from every plate.

The main product of arachidonic acid metabolism in the noninfarcted areas of myocardium (seen in Fig. 1N) was prostacyclin (measured as 6-keto PGF1α, the nonenzymatic breakdown product of PGl2). The production rate of 31.7 pmol/mg per hr represents approximately 1.5% conversion of the initial arachidonic acid substrate. Significant production of PGE2 and PGF2α was also seen in lesser amounts. The co-products of thromboxane synthetase, TxB2 and HHT, were present in a minor, but significant (P < 0.05 above boiled enzyme control), amount and are probably the result of platelets which inevitably get trapped within the tissue. These noninfarcted values also serve as the sham-operated controls since they are all obtained from hearts which would have undergone any nonspecific surgical trauma or inflammation. In addition, the results obtained in normal regions of noninfarcted hearts were identical to those found in control hearts removed from animals without previous infarction or surgery. Differences in the synthetic rates of normal left ventricle controls between 3 days, 3 weeks, or 3 months of convalescence were not apparent.

By 3 days after infarction, there were increases in the production capacity of several products within the infarct zone (Fig. 3). The production of 6-keto PGF1α increased by 126% from 31.7 to 71.7 pmol/mg per hr (P < 0.05). The activity of thromboxane synthetase in the tissue was also significantly increased by 144% from 30.7 to 73.7 pmol/mg per hr. The increase in thromboxane synthetase at this time interval may be due to trapped platelets within the infarcted myocardium. Electron microscopic examination of the 3-day infarcted tissue did reveal platelet aggregates within
the vascular spaces. Less pronounced but significant changes were also seen in PGE$_2$ formation, but no increase was seen in PGF$_{2\alpha}$ production.

At 3 weeks after infarction, the production rates remained elevated in the infarcted zone despite a shift in the invading cell population from neutrophils which were prominent at 3 days to activated fibroblasts, blood vessels, and macrophages. The production of 6-keto PGF$_{1\alpha}$ and the activity of thromboxane synthetase were still elevated compared to the noninfarct left ventricle microsomes and the open bars represent the values for 3 days (n = 6), 3 weeks (n = 8), and 3 months (n = 3) of postinfarction time, respectively. The activity of thromboxane synthetase is expressed as the sum of TxB$_2$ and HHT production.

The 3-month postinfarction time point was designated to represent the "resolved" infarct phase when the tissue had become almost exclusively a collagenous scar. Examination of the tissue from the three dogs that survived for 3 months revealed a marked decrease in the cellularity and vascularity of the granulation tissue. However, fibroblasts and vessels were still present in the infarct zone 3 months after coronary occlusion. This may account for the observation that, although highly variable, the metabolic capacity of the tissue 3 months after infarction is still elevated above noninfarcted left ventricle to levels comparable to those seen at 3 days or 3 weeks (Fig. 3). One dog was studied at a point 5 months after infarction. This tissue did show decreased thromboxane synthetase activity to approximately 50% of the 3-month value (45.8 pmol/mg per hr) and formation of PGE$_2$ (18.4 pmol/mg per hr) but continued to show elevated 6-keto PGF$_{1\alpha}$ production (72.8 pmol/mg per hr) similar to that seen at the other three time intervals. Thus, these results suggest that the arachidonic acid metabolic capabilities of the tissue decrease once the infarct has been totally resolved.

The presence of thromboxane synthetase in the tissue was studied further with the use of a specific thromboxane synthetase inhibitor. The net change in product formation due to addition of imidazole (5 mm) is shown in Figure 4. Imidazole decreased the formation of thromboxane synthetase products at each time interval. The fact that this decrease is significant only at 3 weeks may indicate that—although early tissues may have variable numbers of trapped platelets within the tissue—at 3 weeks, there is a process occurring in the tissue which consistently is accompanied by thromboxane synthetase activity independent of platelet invasion. The increase in 6-keto PGF$_{1\alpha}$ production may be due to "shuttling" of the endoperoxide substrate into prostacyclin production. Only minor changes are seen with imidazole in PGF$_{2\alpha}$ or PGE$_2$ formation. The one significant decrease in PGE$_2$ may represent contamination of the PGE$_2$ area with thromboxane, since imidazole does not inhibit PGE$_2$ isomerase, and since these two products migrate close to one another in the TLC separation.

Discussion

The present results demonstrate that, in microsomes prepared from dog myocardium at different times after infarction, there is an augmented ability to metabolize exogenous arachidonic acid into several metabolic products. This increase occurs throughout the healing process when the tissues are first infiltrated with neutrophils and then with macrophages, blood vessels, and fibroblasts. There are several cell

![Figure 3](http://circres.ahajournals.org/DownloadedFrom/figure3.jpg)

**Figure 3.** The production of arachidonic acid metabolites by noninfarcted and infarcted canine cardiac microsomes at 3 days (3D), 3 weeks (3W), or 3 months (3M) after coronary occlusion. Production is expressed as picomoles of product formed per milligram of microsomal protein for the 1 hour of incubation. The shaded area represents the pooled (n = 17) values from noninfarcted left ventricle microsomes and the open bars represent the values for 3 days (n = 6), 3 weeks (n = 8), and 3 months (n = 3) of postinfarction time, respectively. The activity of thromboxane synthetase is expressed as the sum of TxB$_2$ and HHT production.

![Figure 4](http://circres.ahajournals.org/DownloadedFrom/figure4.jpg)

**Figure 4.** The effect of imidazole on arachidonic acid metabolite production in cardiac microsomes from noninfarcted and 3-day, 3-week- or 3-month-infarcted tissues. Bars represent the net change in product formation caused by the addition of the thromboxane synthetase inhibitor imidazole (5 mm) to the reaction mixtures. Starred values represent significant (P < 0.05) enhancement or inhibition of product formation. The increase in 6-keto PGF$_{1\alpha}$ production may be due to "shuttling" of the endoperoxide substrate away from thromboxane synthetase and into prostacyclin synthetase.
types involved in the resolution of a myocardial infarct and they all possess some ability to metabolize arachidonic acid.

The first cell to invade an area of acutely infarcted myocardium is the polymorphonuclear leukocyte. It enters the infarct 12–24 hours after ischemic necrosis and gradually increases in number during the next few days. Thereafter, the polymorphonuclear leukocytes degenerate until, by the 5th–8th day, few leukocytes are present. Polymorphonuclear leukocytes are able to produce PGE2 and TxB2 (Morley et al., 1979) and could account for the increases in these products seen at 3 days after infarction.

Three weeks after the infarction, the polymorphonuclear leukocytes no longer are present in the infarcted tissue. The infarct is composed of cellular and vascular granulation tissue containing fibroblasts, blood vessels, and macrophages. Of this group, the macrophages probably contribute the most to the biosynthetic potential of PGE2 and TxB2 while the endothelial cells of the neovascular tissue probably contribute to prostacyclin production. By this time, any trapped platelets have disappeared. Thus, it is highly unlikely that the presence of thromboxane is due to residual platelets within the infarct. Myocardial fibroblasts and myocytes in culture (Ahumada et al., 1980) do not synthesize TxA2 and endothelial cells synthesize primarily PGI2. Thus, myocytes and fibroblasts would not be expected to be responsible for the enhanced thromboxane production seen after 3 weeks. Macrophages have been shown to produce PGE2 and TxA2 (Morley et al., 1979) in response to various stimuli and, therefore, may be the cells responsible for the production of these thromboxane synthetase products.

Infarcted regions that are allowed to heal completely consist of nearly cellular and avascular collagenous scars. Since infarcts at 3 months had not yet fully healed, they probably are not indicative of the totally resolved infarct. The results in the 3-month dog suggest that the metabolic capacity does indeed diminish when the scar has fully matured.

The ability of the myocardium to produce TxA2 during the 3-day to 3-month postinfarction period could explain several of the pathophysiological events that occur at this time. TxA2, acting as a platelet aggregator and as a direct vasoconstrictor, would be capable of causing further infarction of surrounding border zones, thus leading to extension of a healing infarct. Alternatively, TxA2 may also have a direct cytotoxic effect (Smith et al., 1981), and this may act directly on immediately adjacent normal myocardium to alter the electrophysiological properties of the tissue and thereby directly initiate ventricular dysrhythmias. Using the specific thromboxane synthetase inhibitor OKY-046 ((E)-3-[4-(1-imidazolylmethyl) phenyl]-2-propenoic acid hydrochloride monohydrate), Sakai et al. (1982) have shown that a decrease in TxA2 production by OKY-046 is accompanied by a decrease in the production of lactate (a marker of ischemia) after left anterior descending (LAD) coronary artery ligation in open-chested dogs. Coker et al. (1982) have found a similar protective effect using the thromboxane synthetase inhibitor UK-37248. The actions of TxA2 generally are opposite to those of PGE2, which has been reported to suppress ventricular dysrhythmias caused by coronary artery ligation in dogs (Zijlstra, 1972). Karmazyn and Dhalla (1980) have reported that PGE2, PGF2α, and PGI2 infusions have strong antiarrhythmic effects in isolated perfused rat hearts; however, they are less effective in guinea pig hearts and ineffective in rabbit hearts. Prostacyclin infusions have been reported to decrease infarct size and prevent ventricular fibrillation after LAD coronary artery occlusion in experimental dogs (Judah et al., 1981; Ribeiro et al., 1981). The general antagonism between TxA2 and PGI2 suggests either a direct cellular arrhythogenic effect mediated by TxA2 or, alternatively, an effect mediated by affecting regional flow heterogeneously within the border and infarct regions and thereby altering the electrical behavior of the tissue.

It is during the period of infarct healing that there is a relatively high increase in the number of sudden deaths, presumably due to lethal ventricular dysrhythmias. By disturbing the balance between the potential beneficial effects of PGI2 and the deleterious effects of TxA2 these invading cells may predispose the tissue to these malignant dysrhythmias. The tissues studied in our investigation represent those of the survivors and thus could be biased in favor of those variants with less TxA2 production and more PGI2 production.

Several treatment regimens have been attempted which could affect this balance. Attempts to reduce inflammation with steroids have resulted in decreased scar formation which ultimately caused myocardial rupture. Aspirin has also been extensively tested to prevent the complications of a previous myocardial infarction and to limit the effects of further infarction. In experiments of acute infarction after LAD occlusion, a rise in thromboxane is seen which is accompanied by ventricular dysrhythmias. When dogs are pretreated with aspirin or UK-37,248 before ligation (Coker et al., 1981a, 1982) there is a fall in both the production of thromboxane and in the frequency of malignant dysrhythmias. Human studies with aspirin (Elwood et al., 1974; Boston Collaborative Drug Surveillance Group, 1974; Coronary Drug Project Research Group, 1976; Elwood and Sweetman, 1979; PARIS, 1980) have been inconclusive as to the protective effects of aspirin. When the results of these studies are pooled, they become statistically significant for a reduction in cardiovascular morbidity (P < 0.0001) and for a decrease in cardiovascular death (P < 0.01) (Lancet editorial, 1980). Although these studies were initially designed for the antiplatelet effects of aspirin for the prevention of subsequent reinfarction, in light of the present findings, it is possible that the beneficial clinical effects on mortality
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could be due to decreasing the deleterious arachidonic acid metabolites produced by invading cellular components of the healing and scarred myocardium and thereby directly attenuating the development of lethal ventricular dysrhythmias.

One interesting effect in our study of the in vitro thromboxane synthetase inhibitor imidazole is the increase seen in the production of 6-keto PGF\textsubscript{1α} commensurate with the decrease in thromboxane synthetase activity (Fig. 4). This presumably is due to "shuttling" of the PGH\textsubscript{2} substrate away from thromboxane synthetase and into prostacyclin synthetase. This effect was seen also with OKY-1581 (sodium-3-[4,3-pyridyl methyl phenyl]-2-methylacrylate) (data not shown); thus, it may be possible, using specific inhibitors of thromboxane synthetase, to shift the production of thromboxane into prostacyclin in vivo for therapeutic benefit.

One factor which this study did not address was the role of leukotrienes or hydroxy fatty acids in regulating the production of thromboxane or prostaglandins. Our chromatographic system did not allow separation of the various mono- or dihydroxy arachidonic acid derivatives, but increases at 3 weeks were seen in the nonpolar band (presumably mono-hydroxy eicosatetraenoic acids) which migrated between HHT and arachidonic acid. Polymorphonuclear leukocytes may be functioning to send chemotactic signals (e.g., leukotriene B\textsubscript{4} or 5-hydroxy eicosatetraenoic acid) which "call in" the macrophages and lymphocytes which are involved in the resolution and healing of the infarct. Understanding the regulatory roles of these products may provide additional avenues of therapeutic manipulation in the future.

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