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Myocardial ischemia possibly mediated by cysteinyl leukotrienes

To the Editor:

Ischemic heart disease manifests itself clinically as a series of syndromes, the pathophysiologic causes of which must be understood if specific treatments are to be designed for specific causes of decreased myocardial oxygenation. We here report that cysteinyl leukotrienes (cys-LTs) can be involved as a cause of myocardial ischemia.

Cys-LTs, derived from arachidonic acid, are produced in excess in patients with aspirin-induced asthma (AIA). In these patients, the key enzyme, LTC_4 synthase, is overexpressed in bronchi, and its mRNA is upregulated in peripheral blood eosinophils.[1] Cys-LTs mediate their biological actions through at least 2 distinct receptors[2]; these are designated *cys-LT$_1$* and *cys-LT$_2$*.

Montelukast, a drug recently introduced for the treatment of asthma,[3] is a specific antagonist of cys-LT_1. An antagonist of cys-LT_2 is not available. In isolated rabbit heart, myocardial ischemia develops as a result of enhanced cys-LT formation, originating from the transfer of leukotriene A_4 from granulocytes to endothelial cells.[4] Atherosclerosis is associated with the appearance of a leukotriene receptor capable of inducing hyperreactivity of human epicardial coronary arteries in response to cys-LTs.[5] Increased cys-LT levels have been described in the urine of patients with coronary artery disease[6] and in coronary blood of patients undergoing angioplasty.[7]

We investigated a 37-year-old man without coronary risk factors who 3 years earlier had developed AIA. The condition was controlled by chronic inhaled corticosteroids and oral prednisone 6 mg. Oral aspirin challenge results were positive: aspirin at a cumulative dose of 118 mg precipitated dyspnea with a fall in FEV_1 of 35%, nasal discharge, headache, and nausea; 2 to 4 hours after the reaction there was an 8-fold (800%) increase in urinary leukotriene E_4 (LTE_4) and a 70% increase in the stable prostaglandin D_2 metabolite 9α11βPGF2. In contrast, rofecoxib 50 mg, a specific Cox-2 inhibitor, was very well tolerated. At base, the LTE_4 urinary excretion, measured on several occasions, was very high (1500-5000 pg/mg creatinine), ranking the patient in the upper 10% of 180 subjects with AIA who were studied by us.

A year before entry, the patient had begun to experience episodes of retrosternal chest pain. With a frequency of 1 to 4 times per week, these occurred when the patient was at rest, each episode lasting approximately 1 minute. The only electrocardiographic abnormality was flat T waves in aVL. Holter monitoring for 24 hours showed short incidents of supraventricular tachycardia (<150/min) and 5 episodes of myocardial ischemia with ST depression and T wave inversion, each lasting 15 to 45 seconds. A coronary artery angiogram showed normal coronary arteries, and cardiac echo was normal.

Because the patient produced excessive amounts of cys-LTs, we investigated the possible role of cys-LT_1 in his myocardial ischemia. We performed 4 exercise tests with the patient on a treadmill (modified Bruce protocol). The patient was premedicated with either montelukast 10 mg or placebo 90 minutes before each exercise test and was blinded to the nature of the therapy.

Results of the 2 placebo tests were negative; the patient completed the protocol with no electrocardiographic ischemic changes. However, when montelukast was given to the patient before the exercise testing, the protocol had to be terminated sooner because of chest pain and changes indicating myocardial ischemia: there was ST-segment depression in leads I, aVL, and $V_{3\text{-}6}$, and there were recurrent episodes of venticular tachycardia, necessitating treatment in the intensive care unit.

Blood was drawn before the exercise stress test and then every 15 minutes for 2 hours after the test for measurement of tryptase and 9α11βPGF_2 by gas chromatography/mass spectrometry; urine was collected over a period of 4 hours for LTE_4 (ELISA).

Results of the placebo-controlled tests showed a rise only in 9α11βPGF_2; this rise, from 7.2 to 12.5 ng/mL, occurred by 45 minutes. The exercise tests preceded by montelukast were accompanied by a rise in 9α11βPGF_2 from 6.4 to 14.5 ng/mL and a rise in tryptase from 6.0 to 7.3 g/L and LTE_4 (Table I), indicating discharge of cys-LTs and enhanced mast cell activation.

Given that the patient's myocardial ischemia was mediated by cys-LTs, he was treated for 4 weeks with a 5-lipoxygenase inhibitor (Zileutone) at a daily dose of 4 × 600 mg. This therapy led to an

TABLE I. Urinary LTE_4 excretion (ng/mg creatinine) after exercise stress testing

	No Zileutone		Following Zileutone
Time of urine collection	**Pretreatment with placebo**	**Pretreatment with montelukast**	**Pretreatment with montelukast**
At base	1804	1523	529
0-2 h	2098	1880	143
2-4 h	1574	2652	143

Placebo or 10 mg montelukast was given 90 minutes before each test.

improvement in FEV_1 of 12%, clearing of the nose, return of the sense of smell, disappearance of the retrosternal pain, and a fall in urinary LTE_4 from 3000 to 450 ng/mg creatinine. Holter monitoring revealed no ischemic episodes. Results of repeated exercise stress testing preceded by 10 mg montelukast showed no evidence of ischemia; blood and urinary parameters studied showed no changes.

This patient had AIA, a distinct clinical syndrome that affects 5% to 10% of adults with asthma but remains largely underdiagnosed.[1] At the biochemical level, AIA is characterized by a chronic overproduction of cys-LTs; our patient excreted very large quantities of LTE_4 in urine, a parameter considered to reflect global cys-LT production. For the following reasons, we believe that massive cys-LT overproduction was the cause of his myocardial ischemia: (1) the classical coronary risk factors were absent; (2) coronary arteries were free of obstruction or other signs of atherosclerosis; (3) attacks of ischemia were accompanied by further increases in urinary LTE_4, already elevated at base; (4) treatment with a 5-LO inhibitor led to a dramatic fall in cys-LT production and disappearance of myocardial ischemia.

We used montelukast as a probe with which to understand the role of the cys-LT_1 receptor in this case. Unexpectedly, the drug precipitated myocardial ischemia during the exercise stress test. Perhaps montelukast, by blocking cys-LT_1, made more cys-LTs available for binding at the second receptor, cys-LT_2, which in contrast with cys-LT_1 is expressed in the heart.[2,6]

Cys-LTs possess a unique pharmacologic profile characterized by potent constriction of microvasculature; they can enhance permeability, reduce coronary blood flow, and reduce myocardial contractility and cardiac output without affecting the heart rate.[8] It has been hypothesized[3,6] that these actions, per se, could one day explain the pathologic process in some cases of angina. Indeed, our report indicates that myocardial ischemia might be caused by enhanced biosynthesis of cys-LTs. Pharmacologic inhibition of cys-LT production—but not blockade of the cys-LT_1 receptor—leads to regression of ischemia.

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