Editorial Comment

Aminophylline for Angina: The "Robin Hood" Effect?*

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In normally perfused myocardium, coronary blood flow is greater within the endocardium than in the epicardium because of greater metabolic activity and oxygen requirements. Adequate perfusion is maintained by local autoregulation with greater vasodilation of endocardial arterioles compared with the more constricted epicardial arteriolar bed (1), with alpha-adrenergic tone probably contributing to maintaining an arteriolar resistance gradient from epicardium to endocardium (2). In coronary artery disease, decreased perfusion pressure distal to an obstructive atherosclerotic plaque in epicardial coronary arteries necessitates even greater endocardial arteriolar vasodilatation to maintain appropriate endocardial oxygen delivery at the cost of further compromising vasodilator capacity. Any intervention that increases myocardial oxygen consumption further dilates the arterioles; the resulting increase in flow creates increased viscous and turbulent energy losses across the obstruction, which lead to a further drop in distal coronary perfusion pressure. This pressure drop compromises perfusion of the maximally vasodilated endocardium because of a redistribution of blood from endocardium to epicardium (transmural "steal") (3-7). Mediators for arteriolar vasodilation probably include adenosine, withdrawal of alpha-adrenergic tone, tissue hypoxia, increased local partial pressure of carbon dioxide (PCo2) and tissue acidosis among other possibilities and may differ for ischemic as opposed to nonischemic myocardium (1).

Aminophylline and coronary artery flow. For many years, adenosine has been known to be a potent coronary arteriolar vasodilator (8), similar in potency to reactive hyperemia after brief coronary occlusion. More recently, antagonism of adenosine-mediated coronary vasodilation by aminophylline has been demonstrated (9). Thus, at first glance, aminophylline would seem to be an unlikely choice as a useful drug in coronary artery disease, where the coronary flow response to stress is already limited. Further, methylxanthines increase myocardial contractility and myocardial oxygen demands. Initial interest in aminophylline for use in coronary artery disease was promoted by interest in its cyclic nucleotide phosphodiesterase inhibitor activity, resulting in increased cyclic adenosine monophosphate with smooth muscle relaxation. In coronary vascular tissue, this would presumably produce vasodilation. However, in intact conscious dogs, aminophylline actually causes an increase in coronary and systemic vascular resistance when infused systemically, a response prevented by alpha-adrenergic blockade (10). Therefore, in contrast to the direct relaxant effect of aminophylline on smooth muscle, the net systemic effect of aminophylline on coronary and systemic vascular tissue is vasoconstriction contributed to by activation or enhancement of alpha-adrenergic receptors, and blockade of adenosine receptors, which mediate vasodilation. The vasoconstrictor impact of aminophylline might be greater in the epicardium, already under tonic alpha-adrenergic influence, in contrast to the endocardium, where vessels are subjected to more autoregulatory vasodilating mediators and less alpha adrenergic tone. Both of these attenuate aminophylline's vasoconstrictor effects.

The "Robin Hood" effect in coronary artery disease. Earlier this year, Picano et al. (11) and Crea et al. (12) independently reported benefit of intravenously administered aminophylline (or theophylline) during exercise of patients with coronary artery disease in blinded, randomized, placebo-controlled studies. Although prolongation in time to onset of angina during exercise (or prevention of angina) might have been due in part to aminophylline's blockade of adenosine-stimulated pain receptors (13), prolongation of the time to ST segment depression and an increase in rate-pressure product at the time of ST segment depression, in addition to significant prolongation in the duration of exercise, suggests a true anti-ischemic effect of aminophylline. Both groups postulated that aminophylline prevented the transmural redistribution of coronary flow from endocardium to epicardium by inhibiting epicardial arteriolar vasodilation during stress. The British group dubbed this the "Robin Hood" effect (12) with blood diverted from the oxygen-"rich" epicardium to the oxygen-"poor" endocardium.

The present study: aminophylline in syndrome X. In this issue of the Journal, Emdin and co-workers demonstrate remarkable improvement in effort duration, rate-pressure product achieved, and symptom response during bicycle exercise with abolition of ischemic-appearing ST segment responses after aminophylline infusion in eight women with syndrome X (defined as anginal chest pain, angiographically normal coronary arteries and ischemic-appearing ST seg-

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ment responses to exercise and dipyridamole infusion. There is mounting evidence that a subset of patients with anginal chest pain, despite angiographically normal coronary arteries, have functionally abnormal coronary arteries (especially small intramural coronary arteries, prompting us to call this syndrome “microvascular angina”) with reduction of vasodilative responses to pharmacologic stimuli (dipyridamole, contrast dye, calcium channel blockers) and stress (rapid atrial pacing, exercise) and a heightened vasoconstrictor sensitivity to ergonovine and cold pressor testing (15-24).

Emdin, et al. (14) argue that aminophylline’s benefit might be due to prevention of transmural redistribution of coronary flow away from endocardium during stress. The hydrodynamic principle supporting this hypothesis, described previously for epicardial coronary disease, might hold true in syndrome X if the obstruction to coronary flow were moved further “downstream” because of inadequately constricted small coronary arteries (25). This hypothesis is speculative in this study because no measure of coronary flow reserve (to stress or pharmacologic vasodilator) was performed before or after aminophylline. Further, methodology is not yet available to accurately quantitate endocardial versus epicardial myocardial perfusion in humans to investigate aminophylline’s effect on perfusion distribution in patients with syndrome X or coronary artery disease.

Implications. With more demonstrations of exercise and symptom benefit in larger numbers of patients (including men) and with oral preparations of aminophylline or theophylline that do not cause unacceptable side effects or toxicity, there may be a major therapeutic option for patients with syndrome X (and coronary artery disease), many of whom continue to experience frequent chest pain despite use of conventional antianginal medications.

References