PHARMACOLOGY OF ACUTE EFFORT ANGINA*

SUMMARY. From the pharmacologic point of view, each of the major types of antianginal agents—calcium antagonists, beta-blockers, and nitrates—seem to act at least in part by an improvement of the myocardial blood supply. The recently elucidated mechanism of action of nitrates, acting on a common pathway with the endothelium-derived relaxation factor (EDRF), suggests an important role for guanylate cyclase and cyclic GMP in maintaining coronary artery patency in patients with coronary atheroma. The efficacy of calcium antagonists, even in effort-induced angina, is in accord with a current hypothesis that physical exercise in the presence of coronary stenosis can cause relative coronary vasoconstriction, or at least, failure of full dilation. Therefore, calcium antagonists all act, at least in part, on the “supply” side of the supply-demand equation. Beta-adrenergic blockers appear to have as their major mode of action a reduction of heart rate, which not only reduces the oxygen demand but, through an anti-ischemic effect, also appears to improve the endocardial blood supply (in relation to the heart rate). Thus beta-blockade indirectly enhances the supply side of the equation. The intriguing situation arises whereby all three major types of antianginal compounds may also act by a common mechanism of anginal relief, namely, improvement in the coronary blood supply, in addition to the diverse mechanisms specific to each type of compound. That conclusion does not mean the “supply” side of the equation can be ignored. Rather, the critical importance of a reduced myocardial blood supply in the production of anginal syndromes is highlighted.

KEY WORDS. beta-blockade, calcium antagonists, angina pectoris, coronary vasoconstriction, metabolic vasodilation, nitrates, anaerobic metabolism

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Angina pectoris is the result of myocardial ischemia, occurring when the oxygen demand exceeds the oxygen supply. Factors determining the myocardial oxygen demand are the heart rate, the afterload, the preload, the contractility, and metabolic factors that “waste” oxygen (Figure 1). The most important of these is usually the heart rate (Stangeland et al., 1986; Guth et al., 1987). When there is heart failure with cardiomegaly, then increased wall stress can become the dominant factor increasing the oxygen demand. On the supply side, the adequacy of myocardial blood flow is crucial. Thus the patency of the coronary arteries, the severity of stenosis, the adequacy of collateral circulation, and the degree of coronary vasoconstriction or localized spasm might all act to regulate myocardial oxygen supply. When the supply is deficient and the demand outstrips the supply, then there is a myocardial oxygen deficit with anaerobic metabolism.

It may be expected that beta-blockers should act in angina largely to reduce oxygen demand, whereas calcium antagonists should act chiefly to increase oxygen supply (in addition to any effect of calcium antagonists on contractile activity, afterload, or heart rate). An important concept is that myocardial ischemia by itself is unable to achieve maximal coronary vasodilation (Pantley et al., 1985), possibly because the effects of metabolic vasodilation are opposed by neurogenic vasoconstriction (Mohrman and Feigl, 1978). Thus, in effort angina, there is not only an increased oxygen demand, but also inadequate coronary vasodilation, which has variably been termed a dynamic coronary obstruction (Epstein and Talbot, 1981), or inappropriate coronary vasoconstriction (Gunther et al., 1979), and is thought to be neurogenic in mechanism (Berkenboom et al., 1986). This proposal gives calcium antagonists a logical mode of action by coronary dilation during exercise. New experimental evidence suggests that beta-blockers might also act at least in part by improving myocardial blood supply (Guth et al., 1987). The major focus of this review will be to examine the newly proposed mechanisms whereby calcium antagonists and beta-blockers may act in effort angina and to contrast such mechanisms with those of nitrates. Hypothetical proposals to alter the metabolic pathways in ischemia are also evaluated. Because of the prominent role of tone in the regulation of coronary vascular supply, and hence the degree of ischemia, the regulation of coronary patency needs prior consideration (Figure 2).

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Regulation of Coronary Vascular Tone

Normally the metabolic needs of the myocardium are catered for by control of the coronary blood flow, which responds to the energy status of the cell (Figure 3). During increased heart work or ischemia, high-energy phosphate compounds are broken down, eventually to yield adenosine, which is thought to be the major mechanism for such coronary autoregulation (Berne, 1963). In addition, there almost certainly are other vasodilators, including potassium, carbon dioxide (Olsson and Bunger, 1987), and possibly ATP (Vial et al., 1986). Thus, myocardial metabolism, sensitive to workload and the prevailing oxygen tension of the medium, self-regulates energy metabolism chiefly by the release of adenosine, which in very low concentrations causes vasodilation and in higher concentrations may inhibit myocardial contraction, thereby being energy conserving. In addition, the release of ATP occurs as a very early event in response to hypoxia. Such released ATP is hypothetically viewed as a precursor for adenosine, providing “on-site” production of adenosine for coronary vasodilation (for review, see Opie and Owen, 1987). Additional adenosine is also released by the conventional pathway of breakdown of ATP to AMP and then to adenosine. The stimulus to the release of superficially located ATP may be proton production. These hypothetical sequences require further substantiation. Thus, by both a myocardial and a vascular-located messenger system, myocardial energy production is tightly coupled to coronary flow regulation.

Vasoconstrictors Versus Vasodilators

Adenosine and ATP, being vasodilators activated by hypoxia or by increased heart work (in the case of adenosine), most oppose the vasoconstrictor influences. ATP is only an indirect vasodilator, acting via the formation of adenosine. Chief among the vasoconstrictor influences is alpha-receptor stimulator acting on both alpha1 and alpha2-postsynaptic receptors. The alpha receptors appear to be those that mediate calcium influx, that is more sensitive to calcium antagonism, although this difference between the alpha-