MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

DALLAS, TEXAS

MAY 8, 1986

THERAPY OF ANGINA PECTORIS:
NEW INSIGHTS BASED ON A BETTER UNDERSTANDING OF PATHOPHYSIOLOGY

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OUTLINE

During the 1960s and 1970s, patients with angina pectoris were treated predominantly with nitrates and beta-adrenergic blocking agents. In the late 1970s, the calcium channel blockers became available in this country, and over the past 7-8 years, they have become popular in the treatment of individuals with various kinds of angina. At the same time, numerous studies have provided new insights into the pathophysiology of the various ischemic heart disease syndromes, including vasospastic angina, chronic stable angina (also called angina of effort), and unstable angina. From this better understanding of pathophysiology has come a more rational approach to therapy. This review attempts to examine (a)the mechanisms by which the antianginal agents that are presently available exert their beneficial effects and (b)the pathophysiology of the various anginal syndromes. A thorough understanding of these concepts should allow us to establish a logical approach to the medical therapy of angina pectoris [1].

MECHANISM OF ACTION OF ANTIANGINAL AGENTS

A. Nitrates The nitrates have been the cornerstone of antianginal therapy for many years. They exert their antianginal action by (a)reducing myocardial oxygen demand and (b)increasing oxygen supply. They reduce myocardial oxygen demand by dilating peripheral veins, thereby diminishing left ventricular preload; to a lesser extent, they decrease left ventricular afterload by dilating the peripheral arterioles [2-4]. Nitrates do not exert a direct effect on heart rate or contractility.

Nitrates may improve myocardial oxygen supply in several ways. First, they inhibit coronary vasospasm in patients in whom dynamic alterations in coronary artery tone are of pathophysiologic importance. Second, they improve collateral coronary flow to areas of myocardium supplied by occluded or severely diseased coronary arteries [5]. Third, they induce a favorable redistribution of blood flow within the left ventricular wall, improving subendocardial perfusion [6,7](Table 1, page 3).

Sublingual nitroglycerin is rapidly absorbed and exerts a peak effect in 3-10 minutes, but its duration of action is only 20-30 minutes. As a result, it is effective in the treatment of acute episodes of angina but is impractical for long-term, prophylactic use. Orally administered, long-acting nitrate preparations, such as isosorbide dinitrate, exert an antianginal effect for 2-4 hours and, therefore, must be administered frequently to be an effective prophylactic agent. Cutaneous nitroglycerin application (in the form of nitroglycerin paste) produces a sustained nitroglycerin

TABLE 1: MECHANISMS OF ACTION OF NITRATES

1. Reduce myocardial oxygen demand by:
   a. dilating peripheral veins (reducing LV preload)[2-4]
   b. dilating peripheral arteries (reducing LV afterload)

2. Increase myocardial oxygen supply by:
   a. inhibiting coronary vasoconstriction
   b. improving collateral coronary flow [5]
   c. inducing a favorable redistribution of blood flow from nonischemic to ischemic regions [6,7]

blood concentration for 3-5 hours, but these preparations are aesthetically difficult to manage, since they often soil the patient's clothing. As a result, patient compliance with nitroglycerin paste is sometimes poor. The recently developed transcutaneous nitroglycerin patches have been received enthusiastically by physicians and patients, since they can be applied once daily and do not soil the patient's clothing. However, in the manner in which they are presently used, their therapeutic benefit is controversial. Their antianginal effects are not sustained during long-term therapy, probably because of the rapid development of nitrate tolerance [8-10].

Nitrate therapy may be accompanied by adverse effects that limit its use in some patients. The most frequent are those related to drug-induced vasodilatation: headache, dizziness, flushing, and orthostatic hypotension. In addition, high-dose oral nitrates may cause gastrointentinal intolerance.

In short, the orally administered long-acting nitrates and nitroglycerin paste are effective in patients with angina pectoris, but the frequency of adverse effects and their short duration of action complicate patient compliance. In contrast, the transcutaneous nitroglycerin patches are easy to use, and, consequently, patient compliance and satisfaction are high; however, their therapeutic efficacy with sustained use is unproved.

B. Beta-Adrenergic Blocking Agents The beta-adrenergic blockers are effective antianginal agents because they reduce the 3 determinants of myocardial oxygen demand-- heart rate (at rest and especially during exercise), left ventricular contractility, and left ventricular wall tension (Table 2, page 4). However, they do not cause coronary vasodilatation and, in fact, may induce vasoconstriction in patients in whom dynamic alterations in coronary artery tone are of etiologic importance [11]. Many studies have

TABLE 2: MECHANISMS OF ACTION OF BETA-ADRENERGIC BLOCKERS

1. Reduce myocardial oxygen demand by:
   a. diminishing heart rate
   b. reducing left ventricular contractility
   c. reducing left ventricular wall tension

demonstrated the antianginal efficacy of the beta-adrenergic blockers [12,13]. In addition, they are effective in reducing the incidence of sudden death and reinfarction during the months following an acute myocardial infarction [14].

The beta-adrenergic blocking agents induce adverse effects in a substantial number of patients [15]. Generalized fatigue and listlessness due to a reduced cardiac output and a direct effect on the central nervous system are common and may be severe. Although these reactions may be less frequent with the more lipid insoluble beta-blockers (such as nadolol and atenolol), they occur to some extent with all of them. Impotence attributable to the beta-adrenergic blocking agents is usually more psychologic than physiologic in etiology; the patient often states that he or she has lost interest in sexual activity rather than the physical ability to perform. Vivid nightmares and unpleasant dreams occur in as many as 15-20% of patients given beta-blockers.

Some patients have concomitant disease entities that serve as relative or absolute contraindications to beta-blocker administration. Patients with bronchospastic lung disease or severe peripheral vascular disease may note a worsening of these conditions when this treatment is instituted. In those with insulin-dependent diabetes mellitus, the administration of a beta-adrenergic blocker may mask the symptoms of hypoglycemia, which were previously used by the patient to signal a fall in blood glucose.

In summary, although the beta-adrenergic blocking agents have been shown to be effective in most patients with angina pectoris, their use is sometimes limited by their ability only to reduce myocardial oxygen demand, by their potential vasoconstrictive influence in patients with coronary vasospasm, and by the frequency of troublesome adverse effects, especially in patients with an active life-style.

C. Calcium Antagonists The calcium- channel blockers exert a beneficial effect on both sides of the myocardial oxygen supply-demand relationship. On the one hand, they augment myocardial

oxygen supply by inducing coronary vasodilatation and preventing the dynamic alterations in coronary tone that may be operative in patients with various anginal syndromes. In addition, they

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TABLE 3: MECHANISMS OF ACTION OF VERAPAMIL AND DILTIAZEM

1. Reduce myocardial oxygen demand by:
   a. diminishing heart rate
   b. reducing left ventricular contractility
   c. reducing left ventricular wall tension

2. Increase myocardial oxygen supply by:
   a. Inhibiting coronary vasoconstriction
   b. Influencing favorably the time course of left ventricular diastolic filling

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may improve oxygen delivery by influencing the time course of left ventricular diastolic filling. On the other hand, the calcium antagonists reduce myocardial oxygen demand by diminishing, to a variable extent, the 3 major determinants of myocardial oxygen consumption (Table 3, above, and Table 4, below). Verapamil and diltiazem-- the so-called "rate-limiting vasodilators"-- cause a nominal fall in heart rate, left ventricular contractility, and left ventricular wall tension. However, nifedipine may cause a reflex *increase* in heart rate and contractility even though it diminishes left ventricular wall tension by reducing afterload.

TABLE 4: MECHANISMS OF ACTION OF NIFEDIPINE

1. Reduces myocardial oxygen demand by:
   a. dilating peripheral arteries (reducing LV afterload)

2. Increases myocardial oxygen supply by:
   a. Inhibiting coronary vasoconstriction

To a certain extent, verapamil and diltiazem provide a beneficial combination of the salutary effects of the nitrates and beta-adrenergic blockers. They prevent coronary vasospasm and may improve collateral flow to underperfused areas of myocardium, thus mimicking the nitrates in their influence on myocardial oxygen supply. At the same time, these rate-limiting vasodilators reduce the determinants of myocardial oxygen demand-- heart rate, left ventricular contractility, and left ventricular wall tension-- in a manner similar to that of the beta-adrenergic blocking agents. This favorable "blend" of augmenting oxygen supply and limiting

oxygen demand makes these agents attractive in patients with various anginal syndromes.

VASOSPASTIC ("VARIANT") ANGINA PECTORIS

A. Pathophysiology The patient with vasospastic (so-called Prinzmetal's "variant") angina develops myocardial ischemia because of a primary reduction in myocardial oxygen supply, which is caused by periodic episodes of spasm of one of the large epicardial coronary arteries [16]. In many of these individuals, the frequency of vasospasm varies greatly from one time period to the next. Thus, the patient with vasospastic angina may have frequent episodes of angina during a period of several days or weeks, after which anginal frequency falls dramatically. In at least 10-15% of patients, transient episodes of coronary vasospasm may be induced by exercise.

The precise mechanisms responsible for coronary arterial spasm have not been elucidated. Most patients with coronary arterial spasm are heavy smokers, and heavy smoking may cause coronary vasoconstriction mediated, at least in part, through alpha-adrenergic stimulation [17]. Histamine and ergonovine have been shown to provoke coronary arterial spasm in atherosclerotic swine and canine models [18,19], and arginine vasopressin, on occasion, has been shown to provoke spasm in patients [20]. Although morphologic evaluations of coronary arteries that have demonstrated spasm during life are few in number, one recent study [21] has shown an increased number of mast cells in the adventitia, thereby leading to speculation that humoral mediators released by infiltrating mast cells, such as histamine, serotonin, and/or prostaglandin D_2, may be responsible for coronary arterial spasm. It seems reasonable to speculate that the exaggerated local contractile response of coronary arterial spasm is caused by the release of a variety of humoral mediators-- thromboxane A_2, serotonin, histamine, arginine vasopressin, and alpha-adrenergic agonists-- in the setting of focal coronary arterial endothelial dysfunction. The mechanisms responsible for such endothelial injury also may vary from one patient to the next but may be immunologically or mechanically mediated. Thus, endothelial injury may set the stage for an exaggerated coronary vascular contractile response (coronary arterial spasm) when the appropriate concentrations of vasoconstrictors occur locally, especially in the setting of diminished concentrations of intrinsic vasodilators (such as prostacyclin or endothelial-derived relaxing factor) or platelet inhibitors (such as tissue plasminogen activator)[22].

THE BELIEVED PATHOPHYSIOLOGIC
MECHANISM OF CORONARY ARTERIAL SPASM

endothelial damage with dysfunction

↓

↑ sensitivity of involved arterial segment to vasoconstrictors

a. thromboxane A_2
b. serotonin
c. histamine
d. arginine vasopressin
e. alpha-adrenergic agonists

↓ production and/or sensitivity of involved arterial segment to vasodilators and platelet inhibitors

a. prostacyclin
b. endothelial derived relaxing factor
c. tissue plasminogen activator

↓

episodic, focal coronary arterial constriction
(coronary arterial spasm)

B. Therapy A number of pharmacologic agents have been shown to be ineffective in patients with vasospastic angina pectoris. Antiplatelet agents, such as aspirin, do not exert any demonstrable effect [23]. Alpha-adrenergic blockade is ineffective [24,25], whereas the beta-adrenergic blockers have been shown to *increase* the duration of ischemic episodes in these patients [11](Figure 1). Presumably, treatment with the beta blockers is detrimental because these agents reduce underlying beta-adrenergically mediated coronary dilatation.

Each of the calcium antagonists-- verapamil, nifedipine, and diltiazem-- has been shown to be highly effective in patients with vasospastic angina, given alone or in combination with long-acting nitrate preparations, such as oral isosorbide dinitrate [26-29]. Regardless of the exact pathophysiologic mechanism of coronary vasospasm depicted above, the calcium antagonists prevent the final occurrence in the proposed chain of events (episodic, focal coronary arterial constriction) by inhibiting smooth muscle

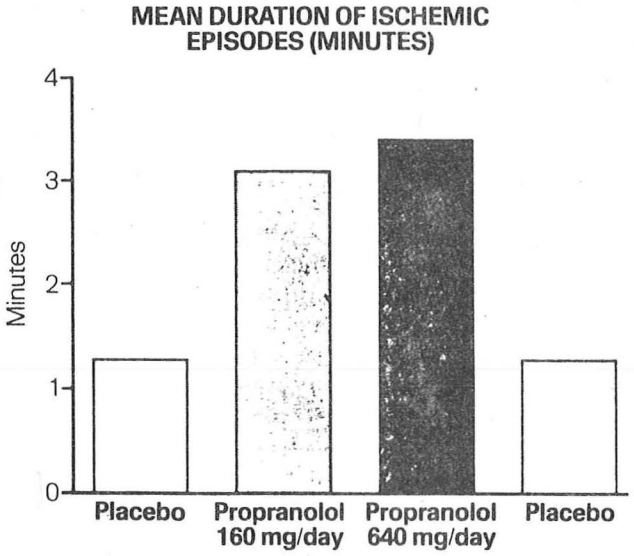
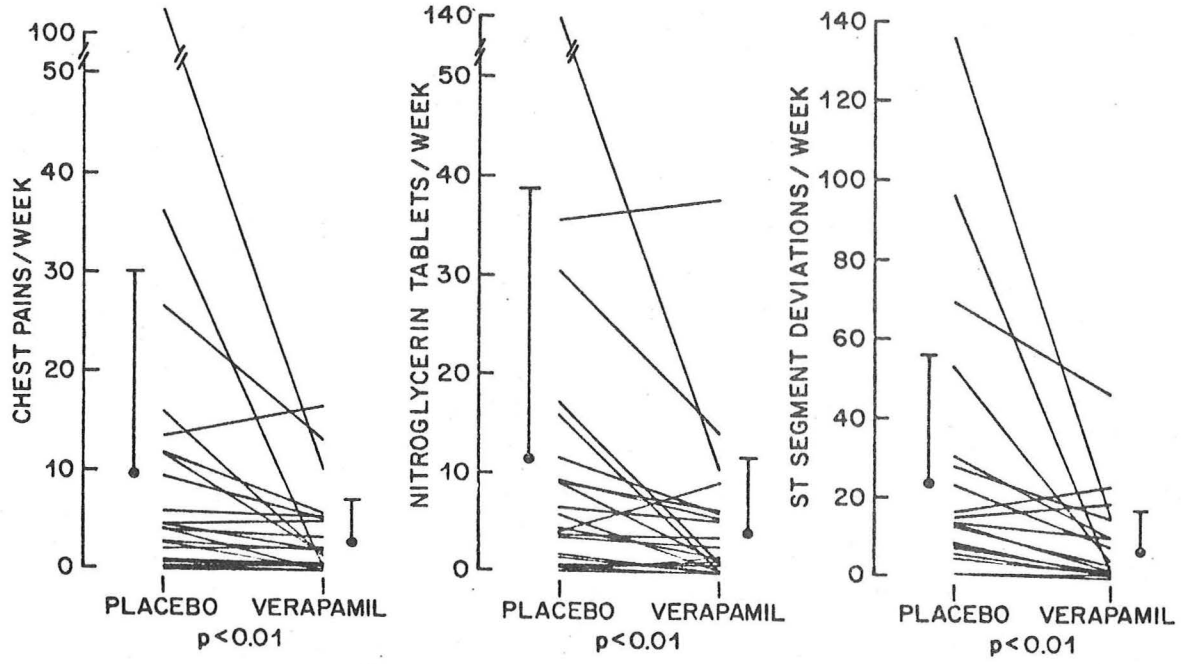


Figure 1 (right): Duration of ischemic episodes in patients with vasospastic angina during placebo, low-dose propranolol, and high-dose propranolol. During beta blocker therapy, the duration of episodes increased. From ref # 11.

Figure 2 (below): The number of chest pains/week (left), nitroglycerin tablets used/week (middle), and ST segment deviations/week by Holter monitor (right) during 4 months of placebo and 4 months of verapamil. In comparison to placebo, verapamil reduced the frequency of all 3 variables. From ref # 26.



contraction within the media of the large epicardial coronary arteries. *The therapy of choice for the patient with vasospastic angina is a calcium antagonist. If angina is not satisfactorily ameliorated on this alone, long-acting nitrates should be added (Figure 2, page 8).*

CHRONIC, STABLE ANGINA PECTORIS (ANGINA OF EFFORT)

A. Pathophysiology For many years, patients with chronic, stable angina pectoris were believed to develop myocardial ischemia because of a transient increase in myocardial oxygen demand (due to physical exertion or emotional excitement) in the setting of limited oxygen supply (due to fixed atherosclerotic coronary artery disease). Angina of effort was thought to be a problem of excessive oxygen demand with limited oxygen supply. It seemed totally rational, therefore, to treat these individuals with an agent which diminished myocardial oxygen demand; hence, throughout the late 1960s and 1970s, the beta-adrenergic blockers were used extensively in these patients. However, recent studies have demonstrated that many patients with chronic, stable angina may develop myocardial ischemia because of dynamic coronary vasoconstriction in the setting of fixed atherosclerotic coronary artery disease. For example, Mudge and his associates [30] showed that exposure to cold leads to an increase in myocardial oxygen demand and, at the same time, a *decrease* in coronary blood flow (Figure 3, page 10) in patients with arteriographic evidence of coronary artery disease. This inappropriate coronary vasoconstriction appears to be mediated by alpha-adrenergic stimulation, since it can be prevented with the alpha-adrenergic blocker, phentolamine (Figure 4, page 11). Furthermore, it can be *potentiated* by the beta-adrenergic blocker, propranolol [31]. Subsequent studies in our Catheterization Laboratory have shown similar findings during cigarette smoking: smoking increases myocardial oxygen demand [32] but causes a concomitant *decrease* in oxygen supply, which is prevented by phentolamine and potentiated by propranolol [17] (Figure 5, page 12). Berkenboom et al [33] have shown that similar events occur during exercise. In short, it appears that numerous daily activities-- such as exposure to cold, cigarette smoking, and exercise-- induce alpha-adrenergically mediated increases in coronary artery tone that limit myocardial oxygen supply and, conceivably, provoke ischemia. Clearly, therefore, chronic, stable angina is a syndrome of *both* (a)increased myocardial oxygen demand in the setting of limited supply and (b)dynamic reductions in myocardial oxygen supply, many of which are induced by common, everyday events.

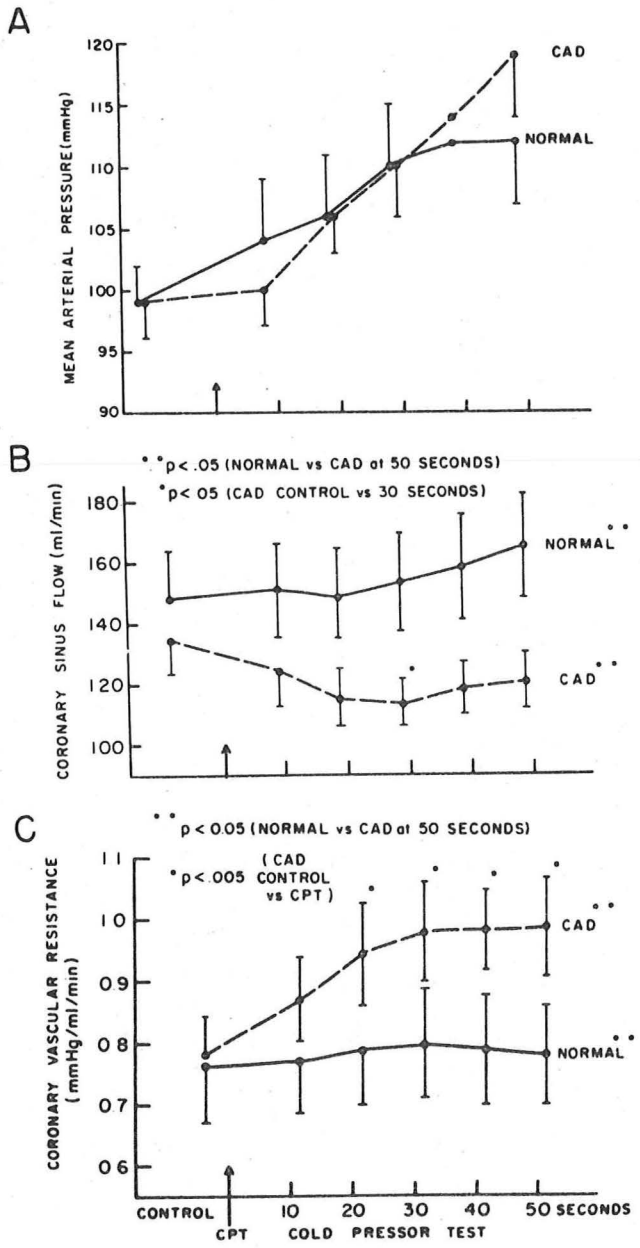


Figure 3: Changes in mean arterial pressure (top), coronary sinus blood flow (middle), and coronary vascular resistance (bottom) before and during immersion of the patient's hand in ice for 50 seconds (the so-called cold pressor test). In those with angiographically normal coronary arteries, mean arterial pressure increased during exposure to cold, and, in response to this increase in oxygen demand, coronary blood flow increased. As a result, coronary vascular resistance did not change during cold pressor testing. In contrast, those patients with coronary artery disease exhibited an increase in pressure during exposure to cold, but coronary blood flow did not rise appropriately. As a result, resistance rose substantially in these patients. From ref # 30.

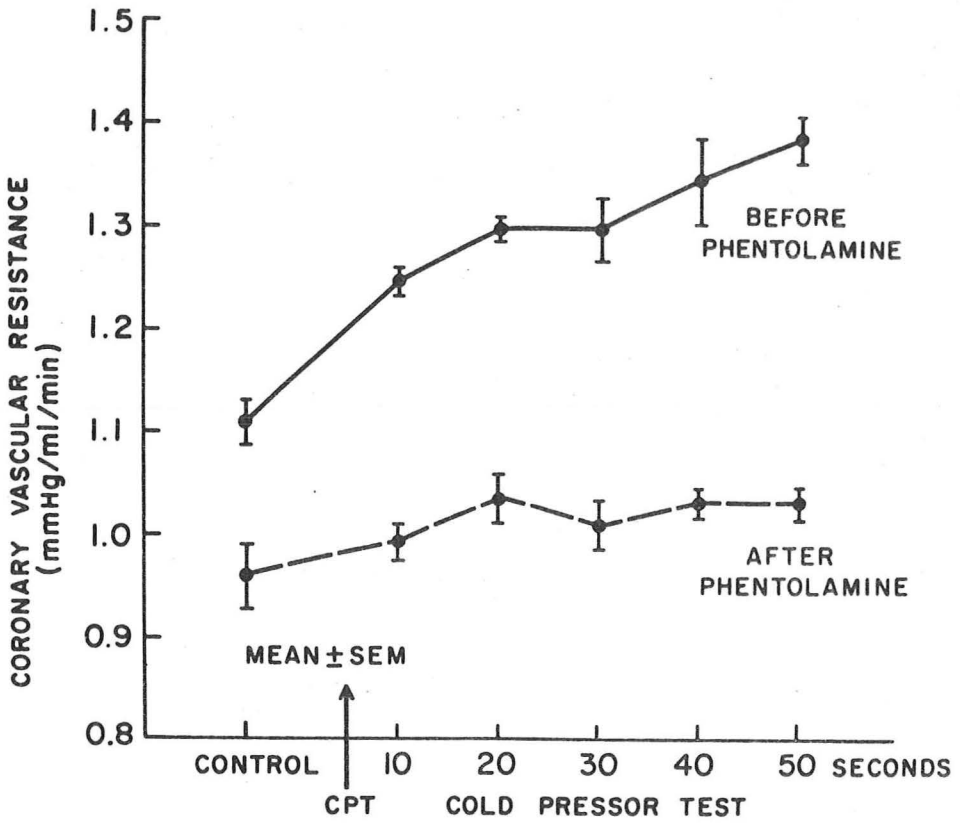


Figure 4: Coronary vascular resistance during the 50 seconds of exposure to cold (the so-called cold pressor test) in the patients with arteriographic evidence of coronary artery disease. As shown in Figure 3 on the previous page, coronary vascular resistance in these individuals rises substantially during cold exposure (solid line, before phentolamine). This inappropriate increase in coronary vascular resistance is prevented by pretreatment with the alpha-adrenergic blocking agent, phentolamine (dotted line). Furthermore, from data not shown here, the inappropriate rise in coronary vascular resistance with exposure to cold is potentiated by pretreatment with the beta-adrenergic blocking agent, propranolol. From ref # 30.

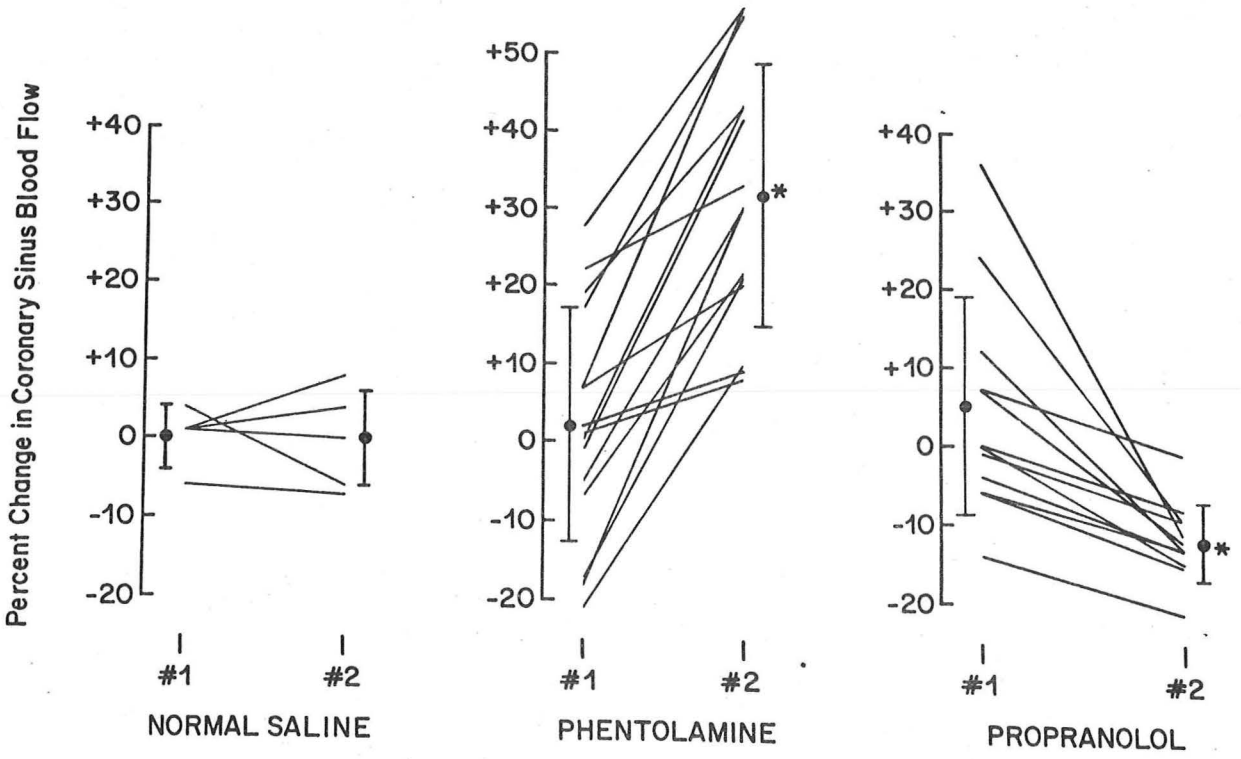


Figure 5: The percent change in coronary sinus blood flow during cigarette smoking both before (labelled # 1) and after (labelled # 2) normal saline (n = 5, controls)(left), phentolamine (n = 15, middle), or propranolol (n = 12, right). Each line represents the data from 1 patient, and the means ± 1 standard deviation are shown on either side of each set of lines. In the control patients, coronary sinus blood flow behaved similarly during smoking before and after saline. In the patients who received phentolamine, coronary sinus blood flow increased substantially during smoking after alpha-adrenergic blockade. In contrast, in the patients who received propranolol, beta-adrenergic blockade caused coronary sinus blood flow to decline during smoking. * $p < 0.01$ in comparison to # 1. From ref # 17.

A. Therapy If, in fact, many patients with chronic, stable angina pectoris develop myocardial ischemia because of (a)enhanced oxygen demand or (b)reduced oxygen supply (due to increased coronary artery tone), the medical therapy of these individuals ideally should be directed at reducing demand *and* improving supply. This can be accomplished with (a)a combination of nitrates and a beta-adrenergic blocker or (b)a rate-limiting vasodilator, such as

verapamil or diltiazem. Numerous studies have shown that these agents are superior to placebo in patients with angina of effort [34,35], and others have shown that verapamil is better than propranolol in this patient population [36]. One can argue effectively, therefore, that many patients with angina of effort obtain adequate control of angina with verapamil or diltiazem monotherapy. These agents are safe, well tolerated, and generally efficacious [37] (Figure 6, page 14).

As single-agent therapy in patients with angina of effort, nifedipine is often accompanied by a reflex increase in heart rate and left ventricular contractility, so that its beneficial influence on myocardial oxygen demand (by reducing left ventricular wall tension) is sometimes negated completely by its effects on heart rate and left ventricular inotropy. In these patients, therefore, nifedipine should be used only in combination with a beta-adrenergic blocker, so that its propensity to induce an increase in heart rate and left ventricular contractile force is blunted or entirely prevented.

In summary, the patient with new-onset angina of effort should, unless contraindicated, be started on single-agent therapy with verapamil, 320-480 mg/day (in 3 divided doses), or diltiazem, 180-360 mg/day (in 3 divided doses). If such monotherapy is not totally effective, long-acting nitrates should be added to the patient's regimen. If a rate-limiting vasodilator/nitrate combination is not adequate, a beta-blocker should be added, provided the patient has no contraindication to the concomitant administration of a rate-limiting vasodilator and a beta-adrenergic blocker. Indeed, a propranolol-verapamil, propranolol-nifedipine, and propranolol-diltiazem combination appears to be highly effective in patients with severe angina of effort [38-41].

NEWLY DIAGNOSED ANGINA OF EFFORT

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monotherapy with a rate-limiting vasodilator
(verapamil, 320-480 mg/day or diltiazem, 180-360 mg/day)

↓

if symptoms continue, long-acting nitrates
(oral or topical) should be added

↓

if symptoms continue, a beta-adrenergic
blocker should be added

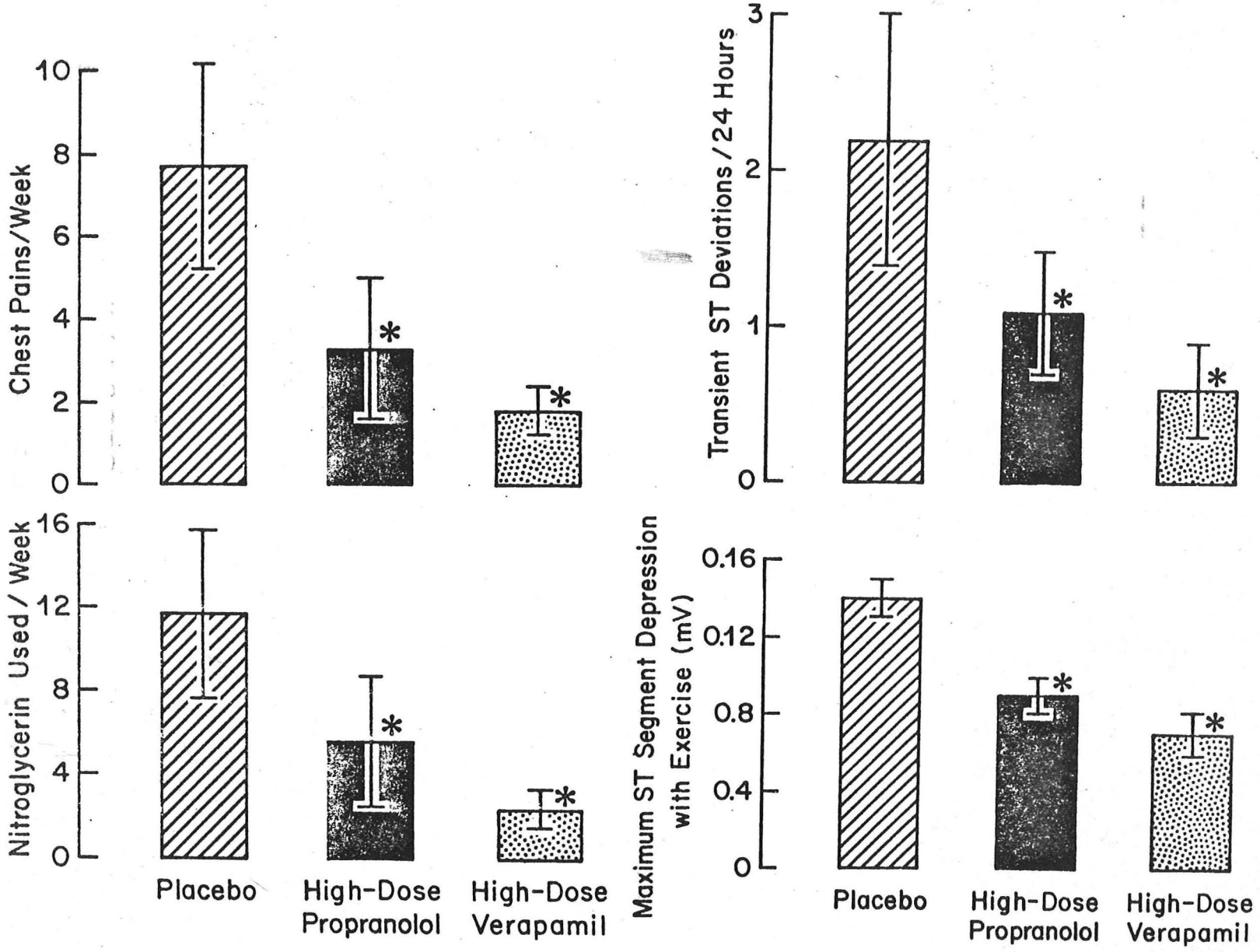

Figure 6: The average number of chest pains/week (upper left), nitroglycerin tablets used/week (lower left), transient ST segment deviations/24 hours (by Holter monitoring)(upper right), and maximum ST segment depression during treadmill exercise (lower right) in 18 patients with angina of effort during treatment with placebo (cross-hatched bars), high-dose propranolol (320 mg/day)(solid bars), and high-dose verapamil (480 mg/day)(stippled bars). Means ± SD are shown. In comparison to placebo, both propranolol and verapamil reduced all 4 variables. * $p < 0.05$ compared to placebo. From ref # 34.

UNSTABLE ANGINA PECTORIS
(CRESCENDO ANGINA, ANGINA AT REST)

A. Pathophysiology The pathophysiology of unstable angina pectoris is almost certainly heterogeneous. On the one hand, some patients develop angina of increasing frequency and severity because a relatively small augmentation of myocardial oxygen demand cannot be met by an appropriate increase in oxygen supply (because of severe atherosclerotic coronary artery disease). Thus, ischemia develops with minimal physical or emotional provocation. On the other hand, some individuals note a worsening of angina because of a primary reduction in myocardial oxygen supply without a change in demand. In these patients, oxygen supply may fall because of (a)coronary arterial spasm or (b)intermittent platelet aggregation at sites of severe atherosclerotic narrowing. In short, unstable angina, in some patients, represents a problem of enhanced oxygen demand in the setting of limited supply; in others, it is a problem of reduced supply due to dynamic changes in coronary artery tone or platelet aggregation within the coronary vasculature.

A number of studies from this institution have suggested that intermittent platelet aggregation in severely diseased coronary arteries, with the release of powerful vasoconstrictors, is of etiologic importance in patients with unstable angina pectoris. In the canine heart in which a severe stenosis of a proximal coronary artery has been created, Willerson and his associates [42-47] have shown that cyclic reductions in coronary blood flow occur because of periodic platelet aggregation at the site of endothelial injury and stenosis. Platelet adherence leads to the release of thromboxane and serotonin, which, in turn, induce vasoconstriction and further platelet aggregation. These repetitive reductions in coronary flow are abolished or substantially attenuated by aspirin [48], dazoxiben (a thromboxane synthetase inhibitor), SQ 29,548 (a thromboxane receptor antagonist), and ketanserin (a 5-hydroxytryptamine receptor antagonist). Thus, thromboxane and serotonin appear to be important in initiating and sustaining cyclic flow reductions in the dog with a severe coronary stenosis.

This elegant canine model may have as its human counterpart many patients with unstable angina pectoris. Studies from our Catheterization Laboratory have demonstrated that patients with unstable angina have high concentrations of thromboxane B_2, the stable metabolite of thromboxane A_2, in coronary sinus blood [49]. Several recent angiographic assessments [50,51] have shown that patients with myocardial infarction or unstable angina demonstrate specific arteriographic morphologic characteristics that are uncommon in lesions of similar severity in patients with chronic

stable angina pectoris. The involved coronary arteries of patients with recent infarction or unstable angina usually demonstrate eccentric, irregular, and roughened stenoses that appear due to (a)disruption of an atherosclerotic plaque or (b)an intraluminal thrombus. It seems reasonable to hypothesize, therefore, that the inciting event leading to acute myocardial infarction or unstable angina is plaque ulceration or disruption, resulting in an area of denuded coronary endothelium. At the site of exposed endothelium, platelet aggregation may lead to (a)cyclic flow reductions, with resultant repetitive and transient episodes of ischemia (unstable angina) or (b)total thrombotic occlusion, with resultant prolonged ischemia or even infarction.

THE BELIEVED PATHOPHYSIOLOGIC
MECHANISM OF UNSTABLE ANGINA PECTORIS

atherosclerotic plaque ulceration

↓

denuded, exposed coronary endothelium

↓

repetitive transient episodes of platelet adherence, with release of vasoconstrictive mediators, such as thromboxane A_2 and serotonin

↓

recurrent episodes of myocardial ischemia at rest

B. Therapy Under ideal circumstances, the medical therapy of the patient with unstable angina should be directed at the underlying cause of myocardial ischemia in that particular subject. However, in the clinical setting, it is usually impossible to define the precise mechanism of ischemia. Therefore, in practical terms, therapy should be aimed at all possible etiologies. First, a rate-limiting vasodilator-- verapamil, 320-480 mg/day, or diltiazem, 180-360 mg/day-- should be instituted to reduce myocardial oxygen demand and to induce coronary vasodilatation in patients in whom periodic increases in coronary artery tone are operative. Several studies have demonstrated that verapamil is effective in patients with unstable angina pectoris, especially in a dose of 480 mg/day [52-54], and similar results have been reported for diltiazem in this patient population [55,56]. Second,

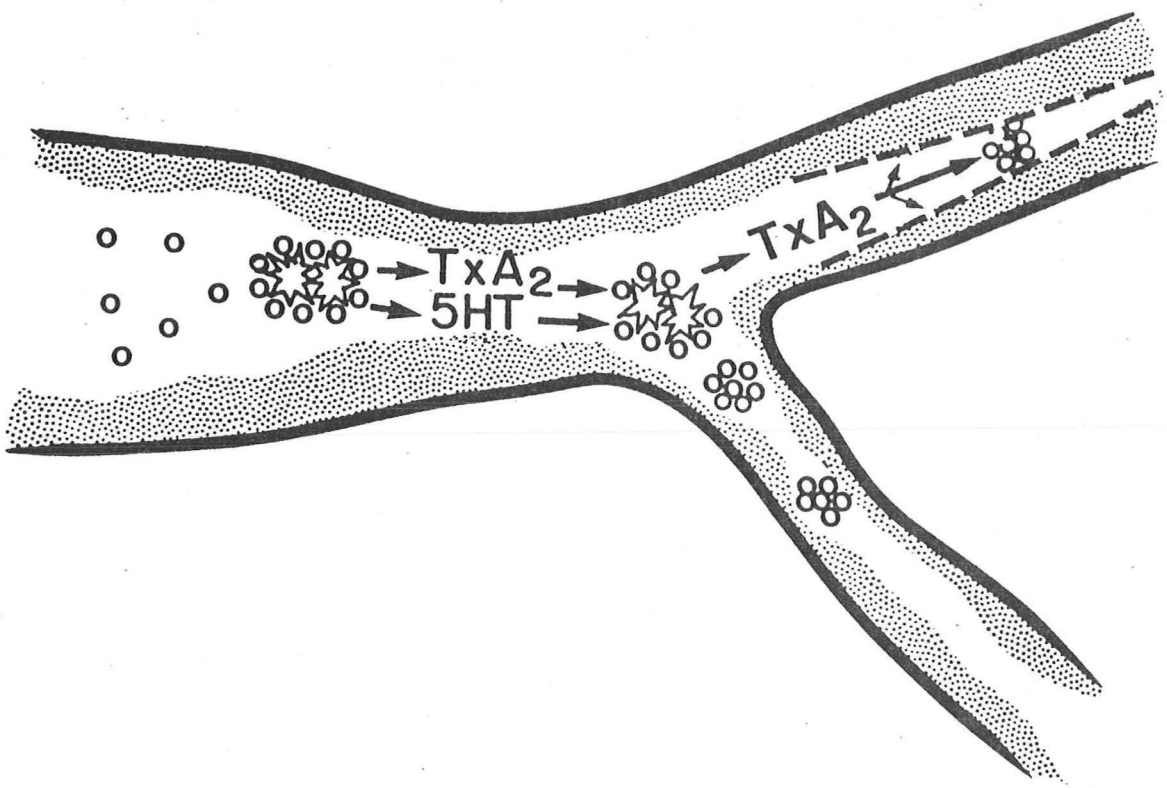

Figure 7: A schematic depiction of one of the possible pathophysiologic mechanisms of unstable angina pectoris. In the coronary vasculature, platelets aggregate at the sites of severe atherosclerotic narrowings. These activated platelets (shown as stars) release thromboxane A_2 (TxA_2) and serotonin (5HT), which, in turn, induce vasoconstriction and further platelet aggregation. From ref # 22.

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long-acting nitrates should be administered in the form of oral isosorbide dinitrate or topical nitrol paste. Third, since platelet aggregation at the sites of severe coronary arterial stenoses is of etiologic importance in many of these patients, an antiplatelet agent, such as aspirin, is warranted. In the canine model of recurrent cyclic flow reductions at sites of critical coronary stenoses, aspirin is highly effective in preventing periodic reductions, whereas heparin exerts no effect [48]. The multicenter Veterans' Administration Hospital study has shown that aspirin, 300 mg/day, reduces mortality and the risk of myocardial infarction in the weeks after an episode of unstable angina [57]. Similar data have been reported

from Canada when a larger dose of aspirin (4 tablets/day) is used (Figure 8, below)[58].

The patient with unstable angina should not be placed on a beta-adrenergic blocker, since coronary vasospasm is of etiologic

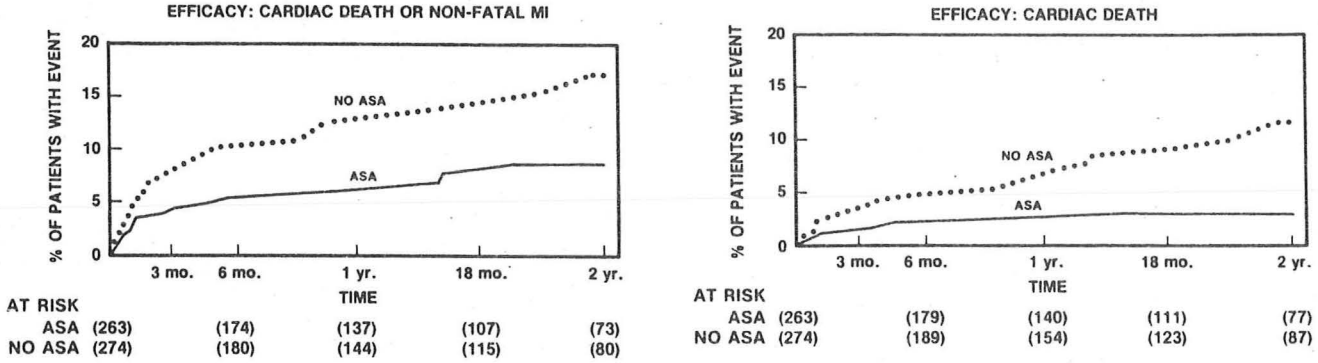

Figure 8: The effect of aspirin on the percentage of patients with (a)cardiac death or non-fatal myocardial infarction (left panel) and (b)cardiac death alone (right panel) over the 2 years after an episode of unstable angina pectoris. From ref # 58.

importance in at least some of these individuals. Parodi et al [59] have demonstrated that propranolol is ineffective in patients hospitalized with pain at rest (Figure 9, below). If the patient with unstable angina has been maintained on propranolol as an outpatient until the time of hospitalization, it should be continued

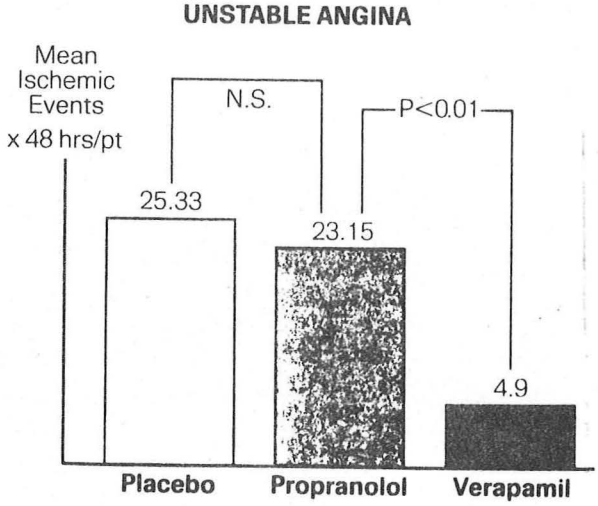

Figure 9: The effect of placebo, propranolol, and verapamil on the number of ischemic events in patients with unstable angina. Note that propranolol exerted no effect in comparison to placebo, whereas verapamil significantly reduced the occurrence of ischemic events. From ref # 59.

at the same dose so as to avoid the possibility of the propranolol withdrawal syndrome [60]. In these subjects, both nifedipine and long-acting nitrates should be instituted immediately in order to prevent propranolol-induced coronary vasoconstriction. The addition of nifedipine and nitrates to propranolol has been shown to be effective in a large, randomized, and double-blind study [61].

Despite adequate therapy with a rate-limiting vasodilator, nitrates, and an antiplatelet agent, an occasional patient with unstable angina continues to have pain. These subjects should promptly receive intravenous nitroglycerin at a reasonable dose, preferably in excess of ½ ug/kg/min. For the average adult, the intravenous nitroglycerin dosage should be at least 35-40 ug/min. If chest pain continues, semi-emergent coronary arteriography should be performed, after which appropriate revascularization (angioplasty or bypass surgery) should be done.

UNSTABLE ANGINA ON NO THERAPY

↓

bed rest
rate-limiting vasodilator
(verapamil, 320-480 mg/day, or diltiazem, 180-360 mg/day)
long-acting nitrates
aspirin, 325 mg/day

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if pain continues: IV nitroglycerin

↓

if pain continues: coronary arteriography & revascularization

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UNSTABLE ANGINA ON BETA-BLOCKER THERAPY

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bed rest
continue beta-blocker
nifedipine, 60-90 mg/day
long-acting nitrates
aspirin, 325 mg/day

↓

if pain continues: IV nitroglycerin

↓

if pain continues: coronary arteriography & revascularization

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CONCLUDING REMARKS

Until about 10 years ago, episodes of myocardial ischemia in patients with chronic, stable angina and unstable angina at rest were believed to occur because of enhanced myocardial oxygen demand in the setting of limited supply. In these individuals, coronary blood flow and myocardial oxygen supply were believed to be fixed by severe atherosclerotic coronary artery disease. It seemed totally rational, therefore, to treat these patients with agents that only reduced myocardial oxygen demand, i.e., the beta-adrenergic blockers, and that exerted little effect on oxygen supply. In recent years, however, it has become clear that patients with angina of effort and unstable angina at rest often develop myocardial ischemia because of primary reductions in oxygen supply, which, in turn, may be caused by dynamic changes in coronary artery tone (coronary arterial "spasm") or platelet aggregation at sites of severe coronary stenoses. The medical therapy of these individuals requires an agent, or combination of agents, which reduces myocardial oxygen demand *and* increases myocardial oxygen supply by (a)causing coronary vasodilatation and (b)preventing platelet aggregation within the coronary vasculature. The realization that most patients with angina, regardless of its clinical features, develop myocardial ischemia because of primary diminutions in coronary blood flow and oxygen supply has altered substantially our approach to effective medical therapy. In short, it has highlighted the importance of giving these patients agents which induce coronary vasodilatation in addition to whatever influence they may exert on myocardial oxygen demand.

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