Medical Therapy of Chronic Stable Angina Pectoris

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Our understanding of chronic stable angina is gradually expanding, and two theories have developed in recent years. First, in patients with chronic stable angina, residual coronary flow reserve can be modulated to an important extent by dynamic changes in the caliber of pliable coronary artery stenoses with preserved muscular media. This theory, coupled with the evidence of the remarkable efficacy of calcium antagonists in variant angina, suggested that these compounds could be very effective in the treatment of chronic stable angina. Second, asymptomatic episodes of ischemia are frequently detected by ambulatory electrocardiographic monitoring, and their causes are likely to be the same as those causing painful attacks.

The results of a careful multicenter, double-blind, crossover study by Stone et al reported in this issue of Circulation, show that nifedipine has no significant anti-ischemic effect and that propranolol is much more effective than diltiazem in preventing asymptomatic ischemia but equally effective in preventing angina. Taken at face value, these observations seem inconsistent with the idea that coronary vasoconstriction contributes to the occurrence of ischemic episodes and that the causes of painful and painless episodes are the same. These apparent discrepancies remind us that we are attempting to prevent ischemic episodes by interfering with varying mechanisms of ischemia that are still incompletely understood. To interpret the intriguing results of the study by Stone et al, it is useful to briefly review the pathogenetic mechanisms of ischemic episodes in patients with chronic stable angina, therapeutic options, assessment of drug efficacy, and significance of asymptomatic ischemic episodes.

Pathogenetic Mechanisms of Ischemic Episodes

Triggers of Ischemic Episodes

A large proportion of patients with a stable pattern of effort-induced angina have a frequent, unpredictable variability of effort tolerance and occasionally even spontaneous anginal attacks at rest. This pattern usually persists unchanged for months and years, in marked contrast to the worsening pattern characteristic of unstable angina. Conversely, patients with an anginal threshold so fixed that they can consistently predict the intensity of effort that will cause angina are less common. Until the late 1970s, the variability of anginal threshold was attributed to either a variable level of myocardial oxygen consumption for the same level of effort or the unreliability of the clinical history because in the presence of coronary atherosclerosis the reduction of coronary flow reserve was thought to be fixed. Subsequently, ambulatory recordings of the electrocardiogram in patients with chronic stable angina showed that the heart rate at the beginning of ischemic episodes during unrestricted daily life could frequently vary by 20 or more beats/min. Ambulatory recordings of arterial blood pressure also showed frequent variations in the heart rate–blood pressure product at 1-mm ST segment depression of 5,000 or more units. The sheer magnitude of this variability of heart rate and heart rate–blood pressure product at the onset of ischemia suggests that in such patients many ischemic episodes, which occur at levels of heart work well tolerated on other occasions, are caused by a transient impairment of coronary perfusion. Therefore, most patients with chronic stable angina have a mixed type of angina pectoris and can develop ischemia either predictably because of excessive effort or unpredictably because of transient impairment of coronary flow.

Modulation of Ischemic Threshold

In patients with mixed angina, ischemic episodes can be caused by three different mechanisms—exclusively by an increase of myocardial oxygen demand that exceeds the maximal residual coronary flow reserve, by a transient reduction of coronary blood flow below resting levels, or by a simultaneous subliminal increase of myocardial demand and a subliminal reduction of coronary flow reserve, both insufficient per se to cause ischemia.

The range over which residual coronary flow reserve can be modulated by occasional vasoconstriction is indicated by the range of variation of heart

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rate or heart rate–blood pressure product between resting level and the maximal level tolerated without developing ischemia in the absence of any superimposed coronary constriction. Therefore, an increase of heart rate relative to 5–10 or 30 minutes before the episode cannot be taken to indicate that ischemia was caused exclusively by increased demand, as this can only be established by comparison with the maximal levels of heart rate lasting for a similar length of time but not associated with ischemia on other occasions. Conversely, a dominant role of transient reduction of coronary blood flow can be suspected in ischemic episodes that occur at a heart rate 20 beats/min or more lower than that tolerated without ischemia on other occasions.

The cause of the variability of ischemic threshold in these patients must be stable, occasional, and unpredictable to account for the stable clinical course and for variability of symptoms. It may result either from dynamic changes in caliber at the site of the stenosis "dynamic coronary stenoses,"11 or by changes in distal coronary vessels. This latter possibility is suggested by the following considerations—only 50% of coronary stenoses in chronic stable angina seem to have a preserved potential for vasomotion10; a persistent impairment of coronary flow reserve and a positive exercise stress test can sometimes be observed after successful angioplasty11,12; and a large variability of ischemic threshold can also be observed in patients with an isolated coronary occlusion and no other stenoses (i.e. without the substratum for dynamic coronary stenoses).13

Besides dynamic coronary stenoses and abnormal vasomotion of distal coronary vessels, aortic pressure and heart rate can also modulate the ischemic threshold because of their effect on the transmural distribution of myocardial perfusion (independently of their effect on myocardial oxygen demand).14 Finally, the ischemic threshold may also be modulated by a maldistribution of transmural myocardial blood flow due to excessive adenosine-mediated coronary dilation of nonischemic territories,15 to β2-adrenergic–induced subepicardial coronary dilation,16 to α2-adrenergic subendocardial vasoconstriction,17 or to changes in prearteriolar vessels similar to those postulated for patients with syndrome X.18

The different mechanisms of altered coronary vasomotion may require a different specific therapeutic approach. However, only two options are currently available in clinical practice—limitation of myocardial oxygen consumption and reduction of coronary vasomotor tone.

Therapeutic Options

Effects of Lowering Myocardial Oxygen Consumption

Lowering of resting myocardial oxygen consumption, and hence resting coronary blood flow, by reducing heart rate, contractility, ventricular volume, and afterload increases the available residual coronary flow reserve, as less is used for the needs of resting flow. A more economic pattern of ventricular pump function increases the amount of physical effort that can be performed without exceeding the maximal residual coronary flow reserve. An increased residual coronary flow reserve and a more economic pattern of cardiac work also reduce the chances that occasional transient subliminal reductions of coronary flow reserve cause ischemia as demand is consistently lower. Therefore, lowering myocardial oxygen consumption may be expected to reduce the number of ischemic episodes not only resulting exclusively from increased myocardial demand but also resulting from a simultaneous subliminal reduction of coronary flow reserve and subliminal increase of myocardial oxygen demand and from a small reduction of resting flow. In contrast, lowering myocardial demand cannot be expected to prevent episodes caused by efforts well above residual coronary flow reserve or by a reduction of coronary flow well below resting levels.

Effects of Reducing Coronary Vasomotor Tone

Prevention of episodic inappropriate coronary vasoconstriction would allow residual coronary flow reserve to always remain at its maximum, which is set by the balance between the limitation of flow caused by atherosclerotic coronary artery obstructions and collateral circulation. A rational treatment should prevent the episodic increase of vasomotor tone in the segment of coronary bed in which it takes place. However, as the cause of vasoconstriction is still unknown at present, ischemic episodes can be prevented only by drugs such as nitrates and calcium antagonists, which reduce vascular smooth muscle tone nonspecifically. Prevention of local episodic coronary vasoconstriction by generalized sustained reduction of vascular smooth muscle tone does not represent an optimal form of therapy. The effect of these drugs may not be sufficient to inhibit completely occasional strong local stimuli or a local enhanced constrictor response as occasionally observed in some patients with variant angina.19 Moreover, in patients with chronic stable angina, the causes of coronary constriction seem to be different from those responsible for occlusive spasm in variant angina;20 therefore, the ability of calcium antagonists to prevent coronary vasoconstriction in the former may be less than in the latter. In addition, coronary vasodilators cannot prevent episodes of ischemia caused exclusively by increased demand.

Assessment of Drug Efficacy

The goals of medical therapy are to improve symptoms, life style, and possibly prognosis. These three goals should be considered separately to assess the overall benefits of therapeutic interventions. The improvement of symptoms can be easily judged by the patient when they are typical, frequent, and severe but not when they are mild and infrequent. The improvement in life style should be assessed not only on the basis of the ability of the patient to sustain normal activities without symptoms but also
on the basis of the inconvenience caused by the treatment and of the emotional impact of the disease. The improvement of prognosis implies the prevention of infarction and death, which are relatively rare in patients with chronic stable angina. Therefore, the beneficial effect of therapy on prognosis is commonly inferred from its ability to prevent or reduce the episodes of myocardial ischemia, painful or painless, objectively documented by exercise stress testing and ambulatory monitoring.

For patients in whom ischemic episodes result from different mechanisms, the anti-ischemic efficacy of a given class of drugs varies in relation to the prevailing cause of ischemic episodes in each individual patient. For ischemic episodes exclusively caused by excessive increase of myocardial demand, it would be unreasonable to expect beneficial effects from drugs that reduce only coronary vasomotor tone, and the rational medical treatment is represented by drugs that allow the heart to work more economically. The efficacy of these drugs in preventing ischemia caused by excessive increase of myocardial demand is best assessed by standardized exercise stress testing.

Conversely, it would seem inappropriate to use exercise stress testing to assess the efficacy of drugs that act by reducing coronary vasomotor tone for two reasons. First, evidence for a substantial limitation of residual coronary flow reserve by increased coronary vasomotor tone during standardized effort test was found in only 30% of 217 patients with chronic stable angina.21 Second, during unrestricted daily life, only some episodes occur at values of heart rate5–7 and heart rate–blood pressure levels8 similar to those at which ischemia develops during the effort test, suggesting that the modulation of residual coronary flow reserve by coronary vasoconstriction is much more prevalent during daily life than during standardized exercise testing. Therefore, in trials, the efficacy of drugs that are thought to prevent ischemic episodes by reducing coronary vasomotor tone is best assessed by their effect on those ischemic episodes that occur at heart rates at least 20 beats/min lower than the maximal level of heart rate sustained for more than 2 minutes without developing ischemia.

**Significance of Asymptomatic Ischemia**

There seems to be sufficient evidence in patients with independently documented coronary disease that episodes of clearly diagnostic ST shift without pain are ischemic. Therefore, the inclusion of painless ST segment episodes in the assessment of drug efficacy improves the statistical analysis of the results, as their number is usually much greater than that of painful episodes. Furthermore, electrocardiographically documented episodes can be better quantified in terms of severity and duration of ischemia.

The significance of painless episodes is variable; it is certainly considerable, regardless of its cause, when ischemia is so severe as to cause acute left ventricular failure or fatal arrhythmias, but it is likely to vary in different syndromes when ischemia is mild. In the same way as anginal pain is much more worrying in unstable than in stable patients and has no apparent prognostic significance in syndrome X, the prognostic significance of painless episodes of transient ischemic ST segment shift should also be different in stable and unstable patients. In stable patients, whether frequent episodes of ischemia, painful or painless, caused by a transient impairment of coronary flow, are an independent indication of instability of the underlying culprit coronary artery lesion is unknown. Also unknown is whether the reduction of frequent episodes of angina by common anti-ischemic therapy (e.g., rest, β-blockers, calcium antagonist, nitrates) improves prognosis as transient, mild ischemia may not cause permanent myocardial damage, and this therapy may not prevent the underlying coronary lesion from becoming unstable.

**Lessons From the Trial**

The study by Stone et al2 provides intriguing information, some of which is at variance with previous studies; it also leaves some questions unanswered. The anti-ischemic efficacy of the drugs assessed in this study, which were used at higher doses than generally recommended, varied according to the method of assessment. First, standardized exercise stress testing indicated that the time to ischemia was increased only from 3.9 minutes on placebo to 4.0 minutes (a 3% increase) by both propranolol and diltiazem and that the amount of ischemia was slightly reduced by all three drugs. Second, angina diaries indicated that the number of anginal attacks per week was reduced from 2.3 on placebo to 1.3 by both propranolol and diltiazem (a 43% reduction). Finally, ambulatory electrocardiographic recordings indicated that the number of ischemic episodes was reduced from 4.6/48 hr during placebo to 2.0/48 hr (a 57% reduction) during propranolol and to 3.8/48 hr during diltiazem (a 17% reduction). The severity and duration of ST segment depression was decreased much more by propranolol than by diltiazem, which is in keeping with the lower nitroglycerin consumption during propranolol.

The minimal improvement on exercise stress testing after propranolol and diltiazem is in sharp contrast with previous reports22–25 and is difficult to explain. The 17% reduction of ischemic episodes on ambulatory electrocardiography after diltiazem is clearly smaller than that observed with propranolol and contrasts with the similar reduction of the two agents in weekly anginal attacks. The absence of significant anti-ischemic effects after nifedipine is also inconsistent with some previous reports4,26 but is in line with others.27 The relatively small efficacy of diltiazem and the lack of efficacy of nifedipine in reducing the number of ischemic episodes per 48 hours could be explained. First, these drugs do not decrease oxygen consumption, as diltiazem produced a much smaller reduction of heart rate than propranolol, and nifedipine increased heart rate; this effect
may have been important for patients with very reduced coronary flow reserve. Second, the generalized reduction of vasomotor tone produced by these drugs may not have been adequate to oppose the localized occasional alteration of coronary vasomotion responsible for some of the ischemic episodes.

The 57% reduction of ischemic episodes during propranolol compares well with the 63% reduction reported by Chierchia et al. in a crossover study using atenolol. The reduction of ischemic episodes on ambulatory electrocardiography by propranolol is much greater than expected on the basis of the 3% increase of time to ischemia during exercise stress testing. This discrepancy is difficult to explain on the basis of available knowledge. The beneficial effects of propranolol on ischemic episodes not caused exclusively by increased demand could be explained by a reduction of myocardial oxygen consumption, as discussed above. However, the reduction of oxygen consumption should also improve effort tolerance unless counteracted by a concomitant detrimental effect not detected in other studies. Alternatively, other beneficial although unknown effects of propranolol on ischemic episodes during daily life should be postulated.

Stone et al.'s study does not report the heart rate at the onset of ST depression during exercise nor the maximal heart rate tolerated by each patient without ischemia. The calculation of an average value of heart rate at the onset of ischemia cannot provide adequate information on the prevalence of episodes caused by an important vasoconstrictor component. Average values are useful to identify the effects of treatment in the presence of measurement inaccuracies and biological variability only when the patients included in the study and the causes of ischemic episodes are homogeneous. When this is not the case, average values may be skewed by the behavior of a few patients with a large number of episodes. The effect of the drugs on ischemic episodes that occurred during daily life at heart rates 20 or more beats/min lower than the maximal tolerated without ischemia on other occasions was not analyzed separately. Therefore, we cannot establish whether the drugs had a different efficacy on those ischemic episodes predominantly caused by a transient reduction of coronary flow reserve and on those episodes predominantly caused by increased demand. Nifedipine, for example, might have increased the number of episodes predominantly caused by increased myocardial demand and reduced the episodes caused predominantly by coronary constriction.

The apparently different effects of propranolol and diltiazem on painful and painless episodes are also difficult to interpret. On placebo, the average number of anginal attacks per week was only 2.3 (no standard deviation was given); therefore, variations in a few patients with a large number of attacks might have skewed the results. The 43% reduction in anginal attacks per week observed during both propranolol and diltiazem treatment might not be statistically different from the corresponding 57% and 17% reductions in ischemic episodes per 24 hours. In Chierchia's study the number of anginal attacks was much larger than in Stone et al.'s study and was reduced to a similar extent as silent episodes.

Finally, the effect of treatment on quality of life was assessed only on the basis of reduction of anginal attacks. Therefore, it is impossible to establish whether the drug most preferred by patients was propranolol or diltiazem as the two had similar antianginal efficacies.

In conclusion, the specific effects of anti-ischemic drugs cannot be correctly interpreted unless patients and ischemic episodes are grouped into homogenous subsets. Until we understand more precisely the causes of ischemic episodes and until anti-ischemic therapy in stable patients is proven to improve prognosis, the choice of anti-ischemic drugs should probably be guided largely by their effects on symptoms and quality of life.

References


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