Conservative Treatment of Coronary Heart Disease

W. Kübler

For the medical treatment of coronary heart disease - i.e. unsufficient myocardial oxygen supply - 3 groups of drugs are nowadays widely used: nitrates, beta-blocking agents and calcium antagonists.

For coronary dilators, such as e.g. dipyridamole, which increase coronary blood flow in a dose dependent manner, no therapeutic benefit has been demonstrated. These drugs induce a reduction of vascular component of coronary resistance. This, however, is in an ischemic myocardial area already at its lowest level as hypoxia is the strongest stimulus for coronary dilatation (for references see KUBLER 1969, 1).

The drugs effective in angina act predominantly by reduction in myocardial energy demands.

1. The nitrates

The drugs most widely used for the interruption of an anginal attack are the nitrates. They reduce myocardial oxygen consumption due to a decrease in preload achieved by venous pooling and due to a less pronounced reduction in afterload. In addition the nitrates improve especially subendocardial perfusion, which is predominantly affected during an anginal attack. This is achieved by reduction in extravascular or myocardial component of coronary resistance and by dilatation of large so-called "conductance" arterioles (2, 3), which predominantly regulate subendocardial blood flow. In contrast to coronary dilators, such as dipyridamole, small arterioles are not affected by nitrates.

The beneficial effects of nitrates in treating angina is, therefore, explained by the combination of reduction in myocardial energy demands and increase in perfusion, especially in the subendocardial layers.

2. The beta-blocking agents

In contrast to the nitrates, which predominantly act on the peripheral circulation, the beta-blockers act on the myocardium itself by inhibition of sympathetic activity, i.e. by a negative chronotropic and negative inotropic effect.

Among the beta-blockers different groups can be differentiated: beta1-blocking agents, with some cardioselectivity, and non-selective beta-blocking agents acting on both beta1- and beta2-receptors. Some beta-blockers have intrinsic sympathomimetic activity leading - apart

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from the inhibiting effect - to some stimulation of beta-receptors. In addition to specific binding to the beta-receptors non-specific binding sites exist, which, however, are only saturated with doses usually not reached under clinical conditions.

The cardioselective beta₁-blockers are preferentially recommended for diabetics, as the antihypoglycaemic effect of catecholamines is still preserved, and for patients with obstructive airways disease, as the bronchi are predominantly supplied with beta₂-receptors. The difference between beta₁- and beta₂-blocking agents, however, is only relative and, therefore, great care is necessary, if beta-blockers are used under these conditions mentioned above.

Beta-blockers with intrinsic sympathetic activity are especially recommended for patients with bradycardia and/or conduction defects. Generally, however, the beta-blocking quality overcomes intrinsic sympathetic activity, so that again great care is mandatory.

Newer findings of our group (4) indicate, that some beta-blockers, such as sotalol, have additional group III antiarrhythmic effects, in otherwise therapy-resistant cases these beta-blockers may well be of special use in the treatment of supraventricular and especially of ventricular tachyarrhythmias.

Beta-blockers block by definition beta-receptors, which are coupled via the coupling factor to the enzyme adenylate-cyclase, which ultimately catalyzes the formation of the second messenger c-AMP. This receptor-enzyme-system is modulated by several factors, such as e.g. GTP/GDP, which act on the coupling factor. Beta-blockers, too, modulate this system by increasing the number of beta-receptors. Sympathetic overactivity observed in some patients after acute beta-blocker withdrawal can be attributed to this increase in receptors. Hence, withdrawal of beta-blockers should be achieved, if possible, stepwise.

Beta-blockers are competitive inhibitors, their action depends on the ratio of beta-blocker concentration to noradrenaline concentration in the synaptic cleft. Under clinical conditions the action of beta-blockers can easily be evaluated by determination of the inhibition of the increase in heart rate and/or blood pressure during exercise or during the administration of beta-stimulants. Using the bicycle stress test it could be shown that the inhibitory effect of beta-blockers on the rise in heart rate stays constant, whereas the inhibitory effect on exercise induced rise in systolic blood pressure decreases with time (5). This is most likely due to counteraction by other pressure systems, allowing in practice a marked reduction in heart rate without pronounced fall in blood pressure and coronary perfusion pressure in the normotensive.

From these data it follows, that the instantaneous action of beta-blockers depends: 1. on the drug concentration at the receptor site, 2. on the sympatho-neuronal and sympatho-adrenal activity, 3. on the number of beta-receptors present, 4. possibly on the modulation of the receptor-adenylate-cyclase complex and 5. on the counteraction, especially by other pressor systems.

3. The calcium-antagonists

This new group of drugs acts by inhibition of the slow inward current (6), i.e., the Ca²⁺-inward or in some tissues the slow Na⁺-current. The calcium-antagonists, therefore, reduce heart rate, they