EFFECTS OF VARIOUS CORONARY VASODILATORS ON MYOCARDIAL OXYGEN CONSUMPTION

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Abstract—Effects of various coronary vasodilators were compared with those of isoprenaline in modified Langendorff's dog heart preparation with cross-circulation by a donor dog. Coronary vasodilators used in this study all induced a significant increase in the rate of coronary blood flow with a decrease in the A-V O$_2$ difference. The coronary vasodilating activity was in the following order; nifedipine>nitroglycerin >iproveratril>dipyridamole, prenylamine, lidoflazine, papaverine>carbochromene, trapymin>visnadin, khellin, which was to 1:1/3:1/10:1/100:1/300:1/1000. These compounds caused a greater increase in the rate of coronary blood flow rather than changes in myocardial oxygen consumption but in a different grade, while isoprenaline caused a vasodilation paralleling an increase in myocardial oxygen consumption. Thus, the ratios of coronary blood flow v.s. myocardial oxygen consumption were approx. graded as follows; nitroglycerin, iproveratril, dipyridamole>nifedipine, lidoflazine, prenylamine, carbochromene, papaverine, visnadin>trapymin, khellin. It is concluded that the vascular smooth muscle of the coronary artery is mainly relaxed by the direct action of these drugs but partly by the indirect metabolic effect on the cardiac muscle. Different mechanisms of relaxation of the coronary artery lead to classification of coronary vasodilators into several different groups.

Since the specific coronary vasodilator effect of khellin was reported by Anrep (1), various compounds termed as coronary vasodilators have been introduced successively in medical science. Although these compounds have in common a distinct coronary vasodilating effect, the mechanism is not the same, as the chemical structure varies with each drug. The method for determination of the dilating effect must therefore be carefully chosen. In the past, Langendorff's preparations of rat, guinea-pig and rabbit hearts were widely used. These preparations, however, were perfused with oxygenated Tyrode's solution in which an oxygen deficiency could not be avoided, therefore the coronary circulation reacted with supersensitive response to drugs.

In order to avoid oxygen deficiency, Dörner et al. (2) measured the coronary sinus outflow by use of Morawitz cannula when they compared the potency of various compounds to produce coronary vasodilation. Nitroglycerin, dipyridamole, papaverine and others were included. On the other hand, Heistracher et al. (3) inserted a catheter into the coronary sinus and measured the oxygen difference between blood samples of the arterial inflow and the coronary sinus outflow collected through the catheters. They estimated the potency of carbochromene, iproveratril and others from arterio-venous oxygen differences, provided that these compounds did not produce any significant metabolic
effect. In order to elucidate the mechanism of drug-induced coronary vasodilation, myocardial oxygen consumption is more important than the simple determination of the rate of coronary blood flow or the arterio-venous oxygen difference. An analysis of the relation between coronary blood flow and myocardial oxygen consumption has, however, not be attempted.

Previously Hashimoto et al. (4, 5) arranged the Langendorff’s dog heart preparation with cross-circulation by a donor dog and examined the effects of drugs on the relation between myocardial oxygen consumption and coronary blood flow in the absence of extracardial effect. They suggested that the relaxation of the coronary circulation without any significant change in cardiac metabolism was the common feature of useful coronary vasodilators.

In this study various coronary vasodilators were examined in the following respects: 1) coronary vasodilating potency. 2) relationship between myocardial oxygen consumption and coronary vasodilation.

MATERIALS AND METHODS

Fifty-four mongrel dogs of both sexes were used including animals from which blood was obtained. Recipient dogs about 10 kg in body wt. were anesthetized with 30 mg/kg of sodium pentobarbital i.v. and donor dogs over 20 kg with 15 mg/kg of morphine and 1 g/kg of urethane s.c. The animals were heparinized by an i.v. administration of 400 U/kg of sodium heparin.

A diagram of the perfusion system is illustrated in Fig. 1. A tracheal cannula was inserted for artificial respiration (Harvard Apparatus Co., Model 607) at the rate of 20
times per min with a tidal volume of 20 ml/kg of air. Arterial blood of a donor dog conducted from the carotid artery was made to flow by the aid of a Dale-Schuster pump into the coronary arteries of the isolated heart of a recipient dog. The Starling pneumatic resistance of 100 mmHg was arranged in parallel to the perfusion system. The perfusion pressure was monitored by an electromanometer (Nihon Kohden, RP-2). The rate of coronary blood flow was determined by the total outflow leaving the pulmonary artery with an electromagnetic flowmeter (Nihon Kohden, MF-2). Arterial and venous blood samples were taken from aortic inflow and pulmonary outflow of 3 ml for a period of 10 sec. Oxygen content was measured by an oxymeter (Instrumentation Lab., Co-oximeter Model 182). Blood sampling during vasodilation was done at the peak response in a volume of 3 ml for a period of 5 sec for short-acting drugs such as nitroglycerin, iproveratril or isoprenaline, but for a period of 10 sec for long-acting drugs such as nifedipine, dipyridamole, prenylamine, lidoflazina, trapymin, papaverine, carbochromene, khellin or visnadin. The myocardial oxygen consumption was expressed as ml per 100 g of wet weight of the heart per min. The heart rate was continuously recorded by a cardiotachometer (Nihon Kohden, RT-2) triggered by the R wave of ECG (lead II) on an ink-writing oscillograph. Technique of the modified Langendorff's dog heart preparation with cross-circulation was utilized as described in a previous paper (5).

Drugs utilized were 1-isoprenaline hydrochloride (Kaken Kagaku), nifedipine (Bayer), nitroglycerin (Nihon Kayaku), iproveratril hydrochloride (Knoll), dipyridamole (Boehringer Ingelheim), prenylamine (Hoechst), lidoflazina (Janssen), trapymin (VEB Deutches Hydriewerk Rodleben), papaverine hydrochloride (Iwaki), carbochromene hydrochloride (Cassella Riedel), khellin (Chyugai) and visnadin (Roger Bellon). A volume of 0.1 ml of a drug solution was injected into a rubber tube connected to the arterial cannula for a period of 10 sec. Stock solutions were made up in the following way: Iproveratril, lidoflazina, carbochromene and isoprenaline were dissolved in 0.01 N-HCl, visnadin with propylene glycol, khellin suspended in distilled water, and other drugs in saline. Desired concentration was obtained by dilution of the stock solution with saline.

RESULTS

1. Control values of rate of coronary blood flow, arterio-venous oxygen difference, myocardial oxygen consumption, ratio of coronary blood flow v.s. myocardial oxygen consumption and the heart rate (Table 1)

Table 1 summarizes control values of these parameters mentioned above which determined the drug action in this study. Changes in these parameters after the i.a. administration of drugs were depicted graphically as a percentage of each control value with the following results.

2. Effects of various drugs on rate of coronary blood flow and the arterio-venous oxygen difference (Fig. 2)

Results are illustrated in Fig. 2. Isoprenaline produced a definite and transient increase in the rate of coronary blood flow. The arterio-venous oxygen difference (A-V
TABLE 1. Control values of cardiac parameters.

| Parameter                                           | Number of animals | Mean±S.E.                  |
|-----------------------------------------------------|-------------------|----------------------------|
| Coronary blood flow rate                            | 18                | 75.0±4.1 ml/min            |
| Arterio-venous oxygen difference                    | 18                | 5.3±0.2ml/100 ml of blood  |
| Myocardial oxygen consumption                       | 18                | 3.3±0.2 ml/100 g of heart/min. |
| Coronary blood flow rate per myocardial oxygen consumption | 18                | 23.3±1.1 ml/100 g of heart/min. |
| Heart rate                                          | 18                | 134.0±2.0 beats/min.       |

Fig. 2. Dose response curves for the coronary blood flow rate (CBF) and arterio-venous oxygen difference (A-V O₂) to various coronary vasodilators. Each dot and vertical bar represent mean and standard error of response to each dose of drugs (n=4 to 8). Ordinates, percent change in CBF (upper curve) and (A-V O₂) (lower curve); abscissae, dose in logarithmic scale. Iso: I-isoprenaline, Nf: nifedipine, N: nitroglycerin, Ip: iproveratril, Pr: prenylamine, D: dipyridamole, L: lidoflazine, Pa: papaverine, C: carbochroinene, Tr: trapymin, V: visnadin and K: khellin. Abbreviation of these drugs and number of experiments are common to Fig. 2-Fig. 4.

O₂ difference) did not change in a dose range from 0.01 to 0.1 µg. Nifedipine, nitroglycerin, carbochroinene, papaverine and visnadin caused, dose-dependently, an increase in the rate of coronary blood flow and a marked decrease in the A-V O₂ difference with increasing doses. Therefore, coronary vasodilating activity of these compounds was compared both at the dose which caused a fifty percent increase in the flow rate of coronary circulation and at the dose producing a twenty five percent decrease in the A-V O₂ difference. When the vasodilating activity of eleven coronary vasodilators was evaluated
from the increase in rate of coronary blood flow, the following order was obtained: nifedipine > nitroglycerin > iproveratril > dipyridamole, prenylamine > lidoflazine, papaverine, carbochromene, trapymin, visnadin, khellin, which was approx. equivalent to 1: 1/3: 1/10: 1/100: 1/300: 1/1000. When coronary vasodilating activity was evaluated from the decrease in the A-V O₂ difference, the following order was obtained: nifedipine, nitroglycerin > iproveratril > dipyridamole > prenylamine, lidoflazine, papaverine > carbochromene, trapymin, visnadin > khellin, which was approx. equivalent to 1: 1/3: 1/30: 1/100: 1/300: 1/3000. Both procedures resulted in approx. the same evaluation of the potency of various coronary vasodilators.

3. Effects of various drugs on myocardial oxygen consumption and heart rate (Fig. 3)

Results are illustrated in Fig. 3. Isoprenaline caused a dose-dependent increase in myocardial oxygen consumption (MVO₂). Prenylamine, trapymin, carbochromene and papaverine caused an increase in the MVO₂ by approx. fifty percent at the dose which caused a one hundred percent increase in the rate of coronary blood flow. Other coronary vasodilators did not show over a fifty percent increase in the MVO₂. The MVO₂ was hardly changed by nitroglycerin, lidoflazine, visnadin and khellin when these compounds induced over a one hundred percent increase in the rate of coronary blood flow. Iproveratril and dipyridamole showed a suppression of the MVO₂ while the rate of coronary blood flow increased over one hundred percent.

![Fig. 3. Dose response curves for the myocardial oxygen consumption (MVO₂) and the heart rate (HR) to various coronary vasodilators. Ordinates, percent change in MVO₂ (upper curve) and HR (lower curve); abscissae, dose in logarithmic scale.](image-url)
Concerning the heart rate, papaverine and trapymin induced dose-dependently positive chronotropic effects, while iproveratril and carbocromene showed a deceleration of heart rate. On the other hand, nitroglycerin, nifedipine, dipyridamole, lidoflazine, prenylamine, visnadin and khellin produced no significant change in the heart rate, even when these compounds induced approx. the maximum increase in the rate of coronary blood flow.

4. Effect of various drugs on the relation between the rate of coronary blood flow and myocardial oxygen consumption (Fig. 4)

Relation between a change in the rate of coronary blood flow and that in myocardial oxygen consumption induced by the twelve drugs is expressed as a change in the ratio of coronary blood flow v.s. myocardial oxygen consumption. The results are summarized in Fig. 4. Isoprenaline did not cause a change in the above-mentioned ratio in a dose range from 0.01 to 0.1 μg, but various coronary vasodilators caused, dose-dependently, with increasing doses, a marked increase in the ratio. Increase in the ratio induced by trapymin and khellin, however, was very slight. Increment of the ratios was observed with lower doses of papaverine and visnadin but changed to a slight decrease in the ratios with large doses of these drugs.

![Fig. 4. Dose response curves for the ratio of coronary blood flow v.s. myocardial oxygen consumption (CBF/MVO₂) to various coronary vasodilators. Ordinate, percent change in CBF/MVO₂; abscissa, dose in logarithmic scale.](image)

**DISCUSSION**

It is generally accepted that coronary blood flow is regulated by the cardiac oxygen consumption over a wide range of cardiac performance (6, 7). Thus, in the physiological state both parameters change in parallel, while in ischemic heart disease, oxygen demand and supply readily loses its balance when various kinds of extra-cardial factors are loaded. Prevention of the occurrence of such unbalance through an increase of the regional coronary circulation is the working hypothesis for research of effective therapeutic agents re-
garding ischemic heart diseases. Thus, the effect of a drug on myocardial oxygen consumption in relation to the coronary blood flow was widely studied in in vivo and in vitro heart preparations. The blood-perfused Langendorff's dog heart preparation used in this study has merit when making a simple comparison of different drugs on coronary circulation and on cardiac metabolism where extra-cardial influence can be avoided.

Isoprenaline is selected as the standard compound rather than various coronary vasodilators as the rate of coronary blood flow is linearly increased in proportion to an increased myocardial oxygen consumption. Isoprenaline did not cause a change in the ratio of coronary blood flow v.s. myocardial oxygen consumption in this study. This result is in accord with that of a previous report (5). On the other hand, all other compounds tested in this study, nifedipine, nitroglycerin, iproveratril, dipyridamole, lidoflazaine, prenylamine, papaverine, carbochromene, trapymin, visnadin and khellin caused a decrease in the A-V O_2 difference while an increase was seen in the rate of coronary blood flow. Although very slight increases in the myocardial oxygen consumption were observed with these drugs, slight decreases in myocardial oxygen consumption were seen when larger doses of iproveratril or dipyridamole were given. It is concluded that the drugs tested in this study caused a greater increase in the rate of coronary blood flow than that in myocardial oxygen consumption. Thus, the vascular smooth muscle of the coronary artery is relaxed mainly by the direct action of these drugs but partly by the indirect metabolic effect on the cardiac muscle.

So many different mechanisms have been proposed in literature concerning the pharmacological properties of these compounds. These coronary vasodilators generally cause an increase in the rate of coronary blood flow without inducing any great change in other peripheral circulations or in cardiodynamics. Furthermore, nitroglycerin dilates the conductance vessel of coronary circulation (8, 9), as well as the large coronary artery (10). It relaxes the smooth muscle of the isolated taenia coli of a guinea-pig due to inhibitory action on the electrical activity of the membrane (11). Dipyridamole (9) and lidoflazaine (10) dilate "the small resistance pre-capillary arteries" and the arterioles, respectively. Papaverine relaxes the smooth muscle of the large blood vessels and has a positive inotropic action (12). Dipyridamole and lidoflazaine potentiate the response of adenosine due to inhibition in uptake of adenosine by erythrocytes (13-15) or blood platelets (16). Carbochromene (17), papaverine (18) and prenylamine (19) relax the smooth muscle through a rise in the cellular cyclic 3', 5'-AMP. Iproveratril (20-22) and nifedipine (23) relax the smooth muscle of vascular beds due to restriction of the transmembrane Ca^{2+} influx during excitation. Prenylamine may release catecholamine as does reserpine (24), while trapymin causes a decrease in toxicity to norepinephrine (25). Visnadin has an anti-spasmodic effect which is approx. similar to that of atropine (26). For these reasons, the mechanism of relaxation of the coronary smooth muscle is probably different among these compounds.

Isoprenaline induces a marked positive chronotropic effect and causes a marked increase in the rate of coronary blood flow and myocardial oxygen consumption (Figs. 2 and 3). Although papaverine and trapymin showed a slight positive chronotropic re-
sponse while iproveratril and carbochromene induced a slightly negative one, each of these drugs caused a greater increase in the rate of coronary blood flow as compared to the change in myocardial oxygen consumption. Either slight cardiac excitation or slight cardiac depression which is suggested by changes in chronotropic responses may modify myocardial oxygen consumption.

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