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ACUTE MYOCARDIAL ISCHAEMIA IN ANAESTHETIZED CATS: EFFECTS OF PAPAVERINE

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1 The effects of papaverine on coronary blood flow, myocardial oxygen consumption, myocardial oxygen tension and the ischaemic ECG pattern were studied in anaesthetized open-chest cats representing three models of acute coronary insufficiency: ligation, spasm, and perfusion of the coronary artery at a stabilized insufficient level.

2 Despite the increase in myocardial oxygen consumption reflecting elevation of oxygen demand, papaverine improved the signs of myocardial ischaemia (the myocardial oxygen tension and ECG pattern), as long as there was a possibility of an increase in blood supply to the affected zone. Where this was excluded, the symptoms were actually aggravated.

3 The results suggest that there is no basis for dividing coronary dilators into 'benign' and 'malignant' according to their ability to increase myocardial oxygen requirements. A coronary dilator enhancing oxygen demand may prove beneficial even following complete coronary artery occlusion.

Introduction

In recent years the important role of coronary arterial spasm in the pathogenesis of angina pectoris and acute myocardial infarction has received significant support from investigations performed in patients with the use of coronary arteriography (Maseri, Mimmo, Chierchia, Marchesi, Pesola & L'Abbate, 1975; Gaasch, Adyanthaya, Wang, Pickering, Quinones & Alexander, 1975; Meller, Pichard & Dack, 1976; Oliva & Breckinridge, 1977). The new data obtained with this method drew attention to the old problem of administering antispasmodics to patients with coronary heart disease.

In the last two decades, therapy has centred on attempts to increase coronary blood flow without increasing oxygen consumption, that is, 'benign vasodilatation' as opposed to that associated with an enhanced myocardial oxygen demand and characterized as 'undesirable' or 'malignant' vasodilatation (Schmidt, 1951). As a result, a number of new potent coronary vasodilators that do not increase myocardial oxygen consumption were developed. However, careful clinical double-blind studies failed to show their efficiency; dipyridamole is the best-known example of this class (De Graff, 1976).

The investigations of Parratt and co-workers have shown that dipyridamole decreases coronary blood flow in the ischaemic regions of myocardium and increases the severity of the ischaemic pattern observed in the electrocardiogram. Two other coronary dilators which also do not increase myocardial oxygen consumption, lidoflazine and carbochromen, have been shown to have similar effects. At the same time oxyfedrine, a coronary vasodilator that enhances myocardial oxygen consumption, increases blood flow through the ischaemic myocardium and reduces the ST segment depression of the electrocardiogram (Parratt, Ledingham & McArdle, 1973; Marshall & Parratt, 1973; 1974).

In view of these facts the problem of 'benign' and 'malignant' vasodilatation is due for reappraisal. In this respect, the classical antispasmodic, papaverine, is of interest as it increases myocardial oxygen consumption (Kisin, 1959; Barner, Kaiser, Hahn, Jellinek, Amako, Lee & Willman, 1972). This effect is possibly associated with a cardiac stimulant action (Simaan & Aviado, 1976).

It was previously concluded that the increase in coronary blood flow that results from papaverine administration is due less to a direct vasodilator action than to increased myocardial oxygen demand (Kisin, 1962). This conclusion was mainly based on two findings. In an isolated cat-heart preparation perfused with donor blood, myocardial oxygen consumption was increased by papaverine to a greater extent than coronary blood flow; against a background of constant-volume perfusion of the coronary vessels, the increase in consumption was due to the enhanced coronary A-V oxygen difference alone.

The present study was undertaken to examine possible conditions under which papaverine, although increasing myocardial oxygen demand, might have a beneficial effect on the symptoms of acute myocardial ischaemia as assessed from electrocardiographic and polarographic evidence.

Methods

The experiments were performed on cats weighing 3–4 kg, anaesthetized with pentobarbitone (30 mg/kg, i.v.) and artificially respired. The heart was exposed through a left thoracotomy and heparin (1.500 iu/kg) was used as the anticoagulant. Arterial pressure was recorded from a femoral artery with a mercury manometer and the heart rate was determined from the electrocardiogram (ECG). The following three models of acute myocardial ischaemia were used:

Ligation of coronary artery

The anterior descending branch of the left coronary artery (LAD), at the boundary between its middle and distal third, was ligated in one stage. This model was used for three groups of experiments.

Group I (11 animals) Coronary sinus outflow, myocardial oxygen consumption and ECG (standard limb lead II) were recorded. Outflow from the coronary sinus was collected with a plastic cannula inserted into the sinus orifice through the right atrium. The coronary venous outflow was recorded continuously and returned to the femoral vein by a pump-flowmeter (Kisin & Tsaturov, 1960). Relative coronary oxygen saturation was also recorded continuously by directing the coronary outflow through a cuvette connected to a transmission-type oximeter. The arterial haemoglobin O_2 saturation was determined by taking arterial samples in the course of the experiment. Venous coronary samples were also taken in order to calibrate the oximeter. The oxygen saturation of the blood samples was measured with a haemoreflector and the haemoglobin content was determined by a photometer. As an index of myocardial oxygen consumption coronary venous flow was multiplied by the arteriovenous difference in oxygen content. The oxygen content was calculated from the saturation, the haemoglobin content and a combination factor of 1.34.

Papaverine was injected 4 to 5 min after ligation of the coronary artery.

Group II (6 animals) Epicardial ECG maps of the left ventricular wall were obtained according to the method of Maroko, Kjekshus, Sobel, Watanabe, Covell, Ross & Braunwald (1971). Saline (0.9% w/v NaCl solution)-soaked cottonwick electrodes were used. Seven to six sites were selected, within the area supplied by the occluded vessel in adjacent areas and in one remote area. Epicardial electrograms were recorded with a Beckman R-611 Dynograph Recorder at a sensitivity of 2 mV = 1 mm and a paper speed of 25 mm/second. ST-segment elevation was measured as the deviation above baseline 0.06 s after the end of the S wave. Severity of ischaemia was considered to be the sum of the ST-segment elevations from all electrode positions (ΣST). A control occlusion was performed with a special clamp in each animal for 20 min and epicardial electrograms were recorded just before and 2, 4, 6, 8, 10, 15 and 20 min after occlusion. After release and return of the electrocardiogram to control values (1 h interval), a second occlusion was carried out. Papaverine was injected 5 min after the second occlusion.

Group III (10 animals) Myocardial oxygen tension was measured polarographically using the method described by Epshtein (1960). The bare tip of the 450 μm insulated copper wire sharpened to a point and amalgamated with mercury acted as a measuring cathode. The reference electrode was a carbon steel needle. The myocardial oxygen-reduction current was measured by a mirror galvanometer (sensitivity 10^{-8} mm of the scale). Two measuring electrodes were inserted into the myocardial wall at a depth of 2 mm, one into the supposed ischaemic zone and the other into a normal zone. Ligation of the coronary artery was performed 20 min after the insertion. Papaverine was injected 5 min after ligation.

In all three groups of animals papaverine was injected intravenously in doses of 1–2 mg/kg.

Spasm of coronary artery

The circumflex or descending branch of the left coronary artery was perfused under constant pressure with the blood from a cannulated carotid artery by a pump-flowmeter (Kisin, 1964). As reported originally by Schofield & Walker (1953) constant pressure perfusion leads to a significant reduction of coronary inflow. In the most of our own experiments the inflow decreased by 50 to 70% for the first 10 to 15 min and this reduced level was maintained throughout. The decreased coronary inflow was accompanied by electrocardiographic evidence of myocardial ischaemia (chiefly elevation of the ST segment). In several cases the initial level of blood flow recovered spontaneously after 1.5–2 hours. Papaverine was injected intravenously in a dose of 2 mg/kg, 20 to 30 min after the beginning of the perfusion (9 experiments).

Perfusion of coronary artery at stabilized insufficient level

The circumflex or descending branch of the left coronary artery was supplied with blood from the carotid artery via a polyethylene tubing system. The blood flow was maintained by means of a pump providing constant flow perfusion. The perfusion volume was gradually decreased to the point of evident myocardial ischaemia, after which the same level was maintained throughout the experiment. The drug was injected into the perfused coronary artery in doses of 0.1 and 0.3 mg (4 experiments).

Values quoted in the text are means ± s.e. mean. Statistical analysis of the results was performed with Student's *t* test for paired data.

Results

Coronary artery ligation

Ligation of the coronary artery in the cats in Group I was followed by a 20 to 30% reduction in coronary sinus outflow and myocardial oxygen consumption. ECG changes consisted chiefly in elevation or (more rarely) depression of the ST segment. The myocardial effects of papaverine under these conditions are summarized in Table 1. Coronary sinus outflow was enhanced; myocardial oxygen consumption was elevated to a relatively smaller degree since there was a small increase in coronary venous oxygen content. The coronary dilator effect of papaverine was accompanied, in 7 out of 11 experiments, by an improved ECG pattern in limb lead II (Figure 1).

The effects of papaverine on Σ ST segment shifts occurring in the epicardial recordings during coronary occlusion (Group II cats) are depicted in Figures 2 and 3. Papaverine induced a pronounced decrease in ST segment elevation. Five minutes after its administration the ST segment was reduced from 40 ± 5 mV to 20 ± 4 mV. Blood pressure was decreased from 92 ± 6 mmHg to 78 ± 5 mmHg. Heart rate was not changed significantly.

In the animals in Group III, coronary artery ligation caused a 30 to 90% drop in oxygen tension in the ischaemic zone, the reduction being more marked when the electrode was at the centre of the ischaemic zone than when it was closer to the edge. Papaverine usually increased myocardial oxygen tension in the normal as well as in the ischaemic area of the heart but in the ischaemic area the increase was somewhat more pronounced. Figure 4 is representative of the majority of these experiments. In 2 out of 10 experiments papaverine lowered oxygen tension in the normal zone (by 5 and 20%), nevertheless even in these experiments a distinct increase in oxygen tension (by 30 and 70%) was noted in the ischaemic area.

Coronary artery spasm

Figure 5 shows a representative record from this series of experiments. When papaverine was administered against a background of coronary artery spasm, there was electrocardiographic evidence of reduced myocardial ischaemia 2 to 3 min after the injection; this effect was recorded in 7 out of 9 experiments. Normalization of the ECG took place before the blood inflow into the perfused artery increased (because of the extra 2 to 4 min needed for the blood

Table 1 Myocardial effects of papaverine when administered after coronary artery ligation

		After papaverine	
Parameter	*Control*	*1 mg/kg (6)*	*2 mg/kg (5)*
Coronary sinus outflow (ml/min)	8.1 ± 0.6	11.3 ± 0.9**	13.6 ± 1.4***
Arterial O_2 saturation (%)	93 ± 2	92 ± 3 NS	91 ± 2 NS
Coronary sinus O_2 saturation (%)	24 ± 3	28 ± 3*	33 ± 3**
Myocardial O_2 consumption (ml/min)	0.83 ± 0.07	1.12 ± 0.10**	1.24 ± 12***
Mean arterial pressure (mmHg)	97 ± 5	79 ± 7**	68 ± 8***
Heart rate (beats/min)	163 ± 5	168 ± 6 NS	156 ± 7 NS

Values are mean ± s.e. mean. Number of experiments in parentheses.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; NS—not significant.

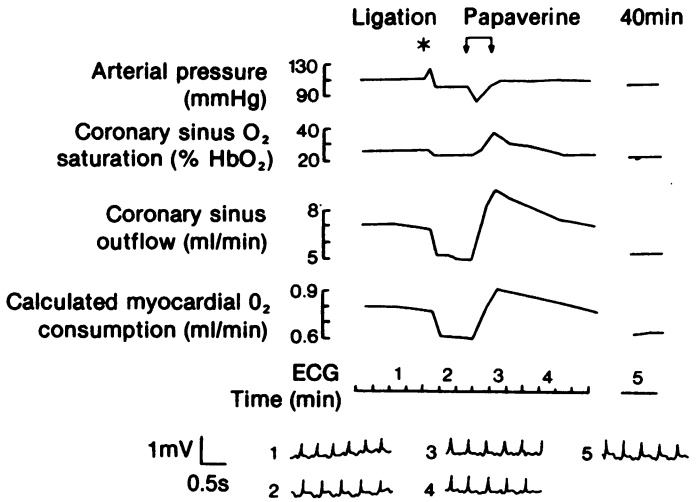

Figure 1 Effects of papaverine (2 mg/kg, i.v.) when given after ligation of the coronary artery in an anaesthetized cat. The figures above the time scale indicate the reading time of the ECG (limb lead II). The right-hand part of the figure shows the values measured 40 min after injection of papaverine.

containing the drug to reach the artery via the pumping system and to dilate it). In some cases further improvement was also observed after the increase in flow.

Perfusion of coronary artery at a stabilized, but insufficient, level

In this series of experiments blood inflow into the perfused coronary artery was maintained at a constant insufficient level and papaverine was injected into the artery. Under these conditions, papaverine aggravated the ischaemic pattern (Figure 6). For comparison chloracyzine (which reduces myocardial oxygen demand, Kisin, 1976) was administered under the same experimental conditions; no deterioration resulted and there was even a slight tendency to normalization.

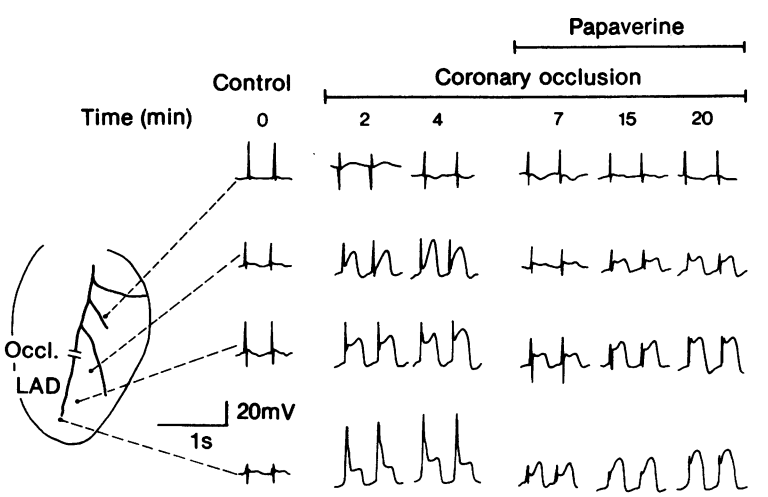

Figure 2 Epicardial electrocardiograms from 4 different sites in a typical experiment. Electrocardiograms were recorded immediately before coronary artery occlusion (time, 0) after the occlusion (2 and 4 min) and (7, 15 and 20 min) after intravenous injection of papaverine (1 mg/kg). Occl = coronary occlusion. LAD = left anterior descending coronary artery.

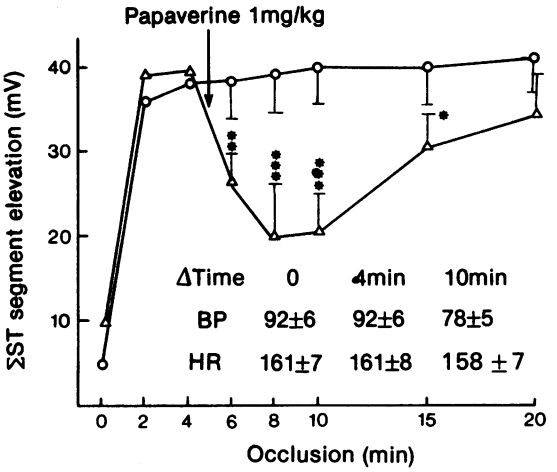

Figure 3 Effects of papaverine (1 mg/kg, i.v.) on the degree of epicardial ST segment elevation during acute coronary artery occlusion. There was a 60 min interval between the first (○) and second (△) occlusions. Papaverine was given 5 min after the second occlusion. BP = mean arterial blood pressure. HR = heart rate at 0.4 and 10 min of the second occlusion. Each point represents the mean results from six experiments and the bars represent the standard errors. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

Discussion

The present study has dealt with three experimental models of acute myocardial ischaemia. In one model (spasm series) it was possibile for a drug to increase both blood inflow into the perfused coronary artery and collateral blood flow. In the ligation series a drug could increase only collateral blood flow. Under conditions of perfusion of the coronary artery at a stabilized insufficient level combined with drug injection into it, the possibility for increase in blood supply of the ischaemic area was insignificant.

In the ligation series of experiments papaverine improved various indices of myocardial ischaemia (myocardial oxygen tension and the ST segment elevation). This agrees well with the results of Mokotoff & Katz (1945) who showed that papaverine reduces the size of myocardial infarction in dogs when given for several weeks after occlusion of a main coronary artery. Normalization of the electrocardiographic pattern also took place in the spasm series of our experiments. The main improvement occurred with the drug spread throughout the myocardial circulation except for the perfused vessels, which were in a state of spasm (the time lag was due to the perfusion system). After the delayed entry of papaverine into the perfusion system there was an increase in blood inflow and a further small additional electrocardiographic improvement. It is reasonable to assume that normalization of the electrocardiographic pattern in the ligation series, as well as the improvement before the increase of blood inflow into the perfused artery in the spasm series, coincides with the dilatation of the coronary vessels around the ischaemic zone. This may then result in an increase in the collateral circulation.

Beneficial effects of papaverine on the various signs of acute myocardial ischaemia took place if there was a possibility of blood flow increase in the ischaemic area. In the experiments where such a possibility was excluded (perfusion of the coronary artery at a stabilized insufficient level) papaverine actually increased the severity of the ischaemic electrocardiographic pat-

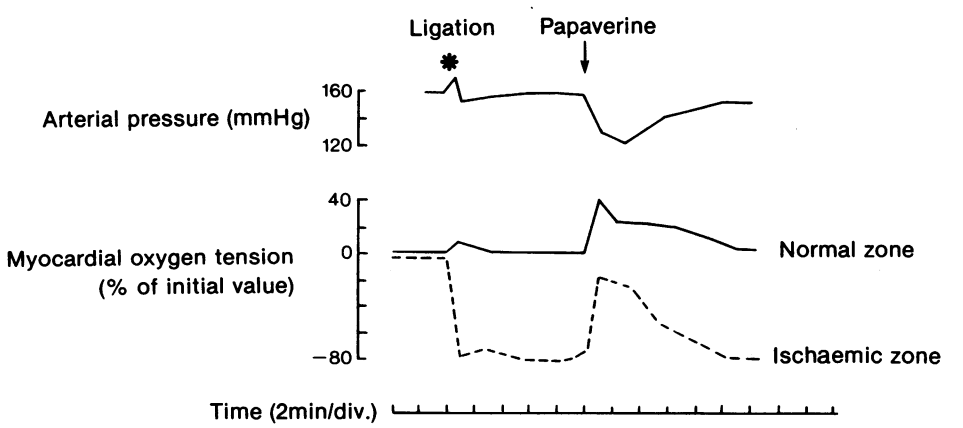

Figure 4 Effects of papaverine (2 mg/kg, i.v.) on myocardial oxygen tension in normal and ischaemic regions of one left ventricular wall in anaesthetized cats. There are considerable and fairly well sustained increases in tension in both regions.

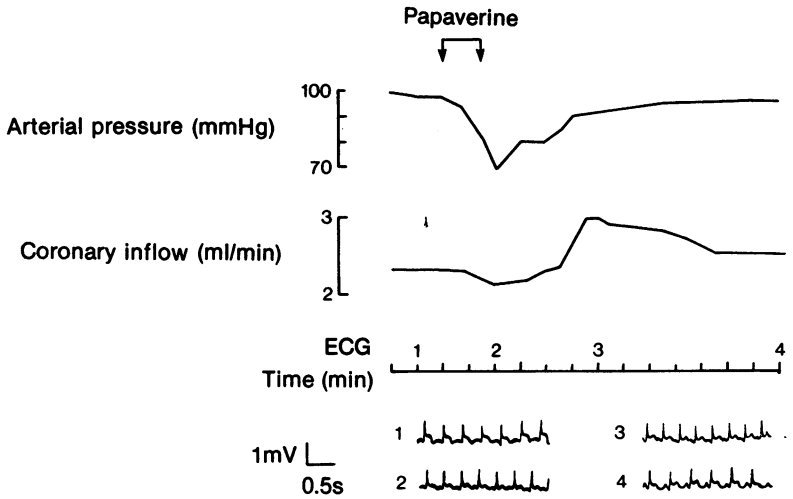

Figure 5 Effects of papaverine (1 mg/kg, i.v.) administered against a background of spasm, on blood inflow into the circumflex branch of the left coronary artery and on the electrocardiogram. The figures above the time scale indicate the moments at which the ECG (limb lead II) was recorded.

tern. It is likely that this detrimental effect was due to the increased myocardial oxygen demand caused by papaverine when there was no possibility of meeting these requirements by increased blood supply. The following statement appears in the second edition of *The Pharmacological Basis of Therapeutics* by Goodman & Gilman (1954): "It remains to be determined whether the increase in coronary blood flow is due mainly to a direct vascular effect of papaverine or in appreciable measure to increase in the work and metabolism of the heart". Since then, a number of workers have shown (see Introduction) that papaverine induces a considerable increase in myocardial oxygen consumption and that its coronary dilator effect depends to a great extent on this property. In the present study it has been shown that papaverine considerably increases total myocardial oxygen consumption following acute ischaemic injury induced by ligation of a coronary artery.

There is evidence that coronary occlusion triggers reflex coronary vasoconstriction mediated through the sympathetic nervous system (Kaverina, 1965; Grayson, Irvine & Parratt, 1971). Thus, whereas overall hypoxia of the heart results in considerable dilatation of the coronary vessels (stronger than the effect of any vasodilator) ischaemia in a limited zone of

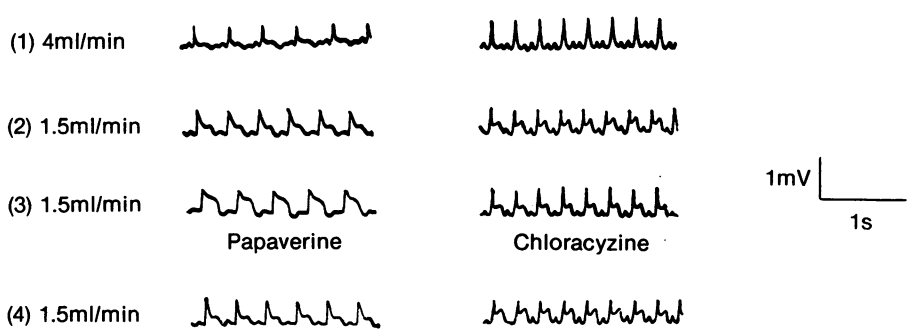

Figure 6 The electrocardiographic effects of papaverine (0.1 mg, i.a.) and chloracyzine (0.3 mg i.a.), during perfusion of the circumflex branch of the left coronary artery at a stabilized insufficient level. (1) Perfusion at 4 ml/min; (2) perfusion at 1.5 ml/min; (3) 2 min after drug administration, at a perfusion of 1.5 ml/min; (4) 10 min after injection, perfusion at 1.5 ml/min.

the myocardium apparently has no vasodilator effect on the surrounding zones and in fact, causes vasoconstriction. Sewell (1965) and Hellstrom (1973) suggested that coronary arterial spasm plays a role in the pathophysiology of acute myocardial infarction. Oliva & Breckinridge (1977) using arteriography have demonstrated coronary spasm in 40% of patients with acute myocardial infarction. On the other hand, after the investigations of Maroko & Braunwald (1976) it became clear that the fate of the acutely ischaemic myocardium is not irrevocably sealed at the time of a coronary occlusion and that it is possible, by a number of interventions, to save jeopardized myocardium. All these facts show that there is a scope for the effect of coronary vasodilators in acute myocardial infarction.

Coronary dilators have been divided into two groups: those that increase myocardial oxygen consumption and those that do not. The first group has been thought to cause 'malignant vasodilatation', the second 'benign vasodilatation'. However, Marshall & Parratt (1973; 1974) have shown that such drugs as dipyridamole, lidoflazine, carbochromen, dilazep (all from the second group) are incapable of increasing flow through a developing infarct and may even divert blood away to the already overperfused normal myocardial regions. In their studies only oxyfedrine (which increased myocardial oxygen consumption) consistently enhanced blood flow through the ischaemic area and improved the electrocardiographic pattern. These authors have suggested that the beneficial effect of oxyfedrine is due to its ability to lower left ventricular end-diastolic pressure.

It has been shown in the experiments described here that papaverine in coronary occlusion increases total myocardial oxygen consumption and improves electrocardiographic and polarographic signs of myocardial ischaemia. These data as well as the data with oxyfedrine show that there is no basis for dividing coronary dilators according to their effect on myocardial oxygen consumption into 'malignant' and 'benign'. Drugs causing 'benign vasodilatation' can worsen ECG evidence of myocardial ischaemia (the experiments of Marshall & Parratt with dipyridamole) and, on the contrary, drugs inducing 'malignant vasodilatation' may give a beneficial effect (oxyfedrine and papaverine).

Positive effects of drugs enhancing myocardial oxygen consumption depends on the possibility that they might also increase blood supply. If there is no such possibility (as in the last series of our experiments with perfusion of the coronary artery at stabilized insufficient level) a drug can cause a detrimental effect. According to the recent data showing an existence of coronary artery spasm in coronary artery disease, coronary vessels retain their capacity for dilatation and there is therefore scope for a beneficial effect of coronary dilators-that-enhance myocardial oxygen consumption.

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