EFFECTS OF CORONARY DILATORS ON SEGMENTAL FORCES IN NORMAL AND ISCHEMIC REGIONS OF THE CANINE LEFT VENTRICULAR WALL

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Changes in segmental forces of contraction (determined by a strain gauge arch) in non-ischemic (normal) and ischemic regions of the same left ventricular wall were studied in dogs anesthetized with morphine and pentobarbital. A branch of the left anterior descending coronary artery was completely occluded, and 10 min after occlusion coronary dilators were injected intravenously. The results can be summarized as follows. 1) Coronary occlusion markedly reduced the segmental force of contraction in the ischemic region, while it did not affect that in the normal region. Heart rate did not change markedly after coronary occlusion. 2) Either nitroglycerin (100 μg/kg) or sodium nitrite (2.5 mg/kg) increased heart rate, and it also increased segmental force of contraction in the normal region while it decreased that in the ischemic region. 3) Papaverine (1 mg/kg) increased heart rate and segmental forces of contraction in both normal and ischemic regions. 4) Dipyridamole (250 μg/kg) slightly increased heart rate, and it also increased segmental force of contraction in the normal region but not in the ischemic region.

The fact that nitrites produce coronary dilatation has been confirmed in normal animals and man. Moreover, it was demonstrated that nitroglycerin did not affect the coronary flow in patients with coronary sclerosis and angina pectoris but did increase it in normal subjects. In our previous study, it was shown in the normal heart that nitroglycerin and papaverine increased the force of myocardial contraction determined by a strain gauge arch. Nevertheless, it is uncertain whether nitrites increase the force of contraction in the ischemic region as well as in the non-ischemic (normal) region.

The present study was undertaken to examine the effects of nitrites on the segmental forces of contraction in the normal and ischemic regions of the same ventricular wall, and to compare the effects of nitrites with those of other coronary dilators, papaverine and dipyridamole.

MATERIALS AND METHODS

Mongrel dogs of either sex, weighing between 7 and 15 kg, were anesthetized by a subcutaneous injection of morphine hydrochloride (10 mg/kg) and morphine, and intubated. A branch of the left anterior descending coronary artery was completely occluded. The results can be summarized as follows. 1) Coronary occlusion markedly reduced the segmental force of contraction in the ischemic region, while it did not affect that in the normal region. Heart rate did not change markedly after coronary occlusion. 2) Either nitroglycerin (100 μg/kg) or sodium nitrite (2.5 mg/kg) increased heart rate, and it also increased segmental force of contraction in the normal region while it decreased that in the ischemic region. 3) Papaverine (1 mg/kg) increased heart rate and segmental forces of contraction in both normal and ischemic regions. 4) Dipyridamole (250 μg/kg) slightly increased heart rate, and it also increased segmental force of contraction in the normal region but not in the ischemic region.

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mg/kg) followed after 30 min by an intravenous injection of sodium pentobarbital (15 mg/kg). After endotracheal intubation, ventilation was maintained by a positive pressure respirator. The thorax was opened at the 4th left intercostal space. One of the branches of the anterior descending coronary artery was dissected free from the surrounding tissues, and a ligation was passed beneath the branch for complete occlusion.

Two small strain gauge arches,7–8 about 0.8 mm long, were sewn on to the same left ventricular wall; one to the region to be made ischemic (ischemic region) by coronary artery occlusion, and the other to the non-ischemic region (normal region) (Fig. 1). Occlusion of the coronary artery continued until the end of each of the experiments. Segmental forces of contraction in the normal and ischemic regions of the left ventricular wall were measured by means of the strain gauge arches, and were recorded on a polygraph. Heart rate was counted from the recorded force tracings.

Animals were divided into four groups according to the drugs injected. The drugs used were nitroglycerin, sodium nitrite, papaverine hydrochloride, and dipyridamole. These drugs were dissolved in a saline solution at the required concentrations, and were injected into the femoral vein over a period of 30 sec 10 min after coronary artery occlusion. (The concentrations of papaverine hydrochloride and sodium nitrite were expressed in terms of salt). The volume of the drug-solution to be injected was 0.5 ml/kg. Values of the segmental forces of contraction were expressed in terms of percent of the control values which were obtained 1 min before the drug injection.

RESULTS

The complete occlusion of a branch of the anterior descending branch of the left coronary artery produced invariably a marked decrease in segmental force of contraction in the ischemic region, but in the normal region it produced only a slight decrease or increase. Similar results have been reported by Schelbert et al.9 In most cases of the present experiments, ventricular arrhythmias and “bulge” were not produced in the ischemic region after coronary artery occlusion. There were a few cases, however, where arrhythmias or “bulge” were observed, but such cases are excluded from the description which follows.

1. Effect of nitroglycerin (Fig. 2)

In the first group of animals, after occlusion

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of the branch of the anterior descending coronary artery, the segmental force of contraction decreased greatly in the ischemic region, and did not change markedly or decreased slightly in the normal region. The degree of the decrease in the ischemic region was more than 20%. Heart rate did not change after coronary occlusion. Nitroglycerin (100 µg/kg) was injected 10 min after coronary occlusion.

The injection of nitroglycerin produced a transitory increase in segmental force of contraction in the normal region, but in the ischemic region it produced a further decrease. Heart rate increased prominently after the nitroglycerin-injection.

2. Effect of sodium nitrite (Fig. 3)

In the second group of animals, after occlusion of the branch of the anterior descending coronary artery, the segmental force of contraction in the ischemic region decreased rapidly by about 20%, whereas in the normal region the segmental force increased slightly. Heart rate increased slightly after coronary occlusion. Sodium nitrite (2.5 mg/kg) was injected 10 min after coronary occlusion.

The injection of sodium nitrite produced a marked increase in the segmental force of contraction in the normal region, but in the ischemic region it produced a further decrease. These results resemble those obtained in the experiments with nitroglycerin.

3. Effect of papaverine (Fig. 4)

In the third group of animals, the segmental force of contraction in the ischemic region decreased by about 15% after occlusion of the branch of the coronary artery, but in the normal region it did not change greatly. Heart rate was little affected by coronary occlusion. Papaverine (1 mg/kg) was injected 10 min after the occlusion.

Following the injection of papaverine, the segmental force of contraction in either normal or ischemic region increased markedly. The increase in segmental forces in both regions reached maximum about 2 min after starting the papaverine injection. Then, the increased forces decreased and tended to return to the control levels. Heart rate was also increased by the papaverine-injection.
Fig. 3. Changes in heart rate and segmental forces of contraction produced by sodium nitrite (2.5 mg/kg, i.v.) in the normal and ischemic regions. Sodium nitrite was injected 10 min after coronary occlusion. Symbols are those given in Fig. 2.

Fig. 4. Changes in heart rate and segmental forces of contraction produced by papaverine (1 mg/kg, i.v.) in the normal and ischemic regions. Papaverine was injected 10 min after coronary occlusion. Symbols are those given in Fig. 2.
4. **Effect of dipyridamole (Fig. 5)**

In the last group of animals, occlusion of the branch of the anterior descending coronary artery produced a marked decrease in segmental force of contraction in the ischemic region, but it produced a slight increase in the normal region. Heart rate was not markedly influenced by coronary occlusion. Dipyridamole (250 µg/kg) was injected 10 min after coronary occlusion.

The injection of dipyridamole produced a moderate increase in segmental force of contraction in the normal region, but in the ischemic region it did not modify the segmental force of contraction. Heart rate was slightly increased by the dipyridamole-injection.

**DISCUSSION**

The contractility of the heart is difficult to define, and many indices to it have been proposed. The force of contraction determined by a strain gauge arch is one of the indices. Hisada pointed out that the strain gauge arch does not measure the force of contraction of the heart as a whole, but it measures the local or segmental force of contraction in the region where the strain gauge is attached. In the present study, two small strain gauges were sewn on to normal and ischemic regions of the same left ventricular wall. Accordingly, the forces obtained in the normal and ischemic regions of the heart may reflect local or segmental forces of contraction in the respective regions. In some experiments, contractile force increased slightly in the normal region after coronary occlusion. This is probably because of an increased activity of the sympathetic nerves produced by ischemia.

It is apparent from the present study that the segmental force of contraction determined by the strain gauge arch is greatly reduced by occlusion of the coronary artery. This result is in good accordance with that of Yoshida, who reported that occlusion of the anterior descending coronary artery produced a decrease in force of contraction, and then produced "bulge" in the ischemic region. In the present study, however, "bulge" was infrequently observed. This is probably because the occluded artery was a small branch of the anterior descending artery, whereas in Yoshida's experiments the occluded artery was the anterior descending branch itself. Darby and Abiko et al. reported that in dogs anesthetized with morphine and pentobarbital the injection of either nitroglycerin or papaverine increased the segmental force of contraction (de-
terminated by the strain gauge arch) temporarily with a concomitant fall in arterial blood pressure and an increase in heart rate. Their findings are similar to those of the present study as far as normal region of the ventricle is concerned. In the ischemic region, however, either nitroglycerin or sodium nitrite decreased and papaverine increased the segmental force. Of particular interest is that either nitroglycerin or sodium nitrite decreased the segmental force only when the myocardial tissue is ischemic. Kirk et al.\(^6\) measured the segmental force of contraction in the epicardium and endocardium separately using two strain gauge arches. They reported that the segmental forces in epicardium and endocardium were reduced by decreasing the coronary flow, and that nitroglycerin injected intracoronary could selectively depress the segmental force of contraction in the endocardium under the conditions of coronary occlusion set at threshold for impairment of contractility.\(^16\) Since the tissue perfusion is more greatly disturbed in the endocardium than in the epicardium by partial occlusion of the coronary artery,\(^17\) it seems that the action of nitroglycerin on the segmental force of contraction depends upon degree of perfusion of the region where the arch was attached. It was reported that nitroglycerin did not reduce the myocardial \(P_O_2\) of the ischemic region.\(^5\) Therefore, a reduction in force of contraction produced by the drug would lead to an improvement of cellular oxidation in the ischemic region. This is probably one of the beneficial effects of nitrates on the ischemic heart.

The action of sodium nitrite on the normal and ischemic regions were similar to that of nitroglycerin. According to Rubin et al., sodium nitrite does not increase but decreases the force of contraction even in the normal heart of the dog anesthetized with pentobarbital alone. In the present study, dogs were anesthetized with morphine and pentobarbital. When morphine is given previously, the dose of pentobarbital enough to produce adequate anesthesia can be reduced to about half the ordinary dose. The discrepancy between the results in the present study and those in the study of Rubin et al.\(^19\) may be due to the differences in the anesthesia.

Both papaverine and dipyridamole are capable of producing a marked increase in the coronary flow in the doses used in the present study.\(^20\) However, papaverine is not considered to be effective against acute myocardial ischemia. One reason for this should be that, as demonstrated in the present study, papaverine markedly increases the segmental force of contraction even when the myocardium is ischemic. An increase in force of contraction requires more oxygen, and therefore the ischemic region will be in a more serious state of oxygen lack. There is a question why ischemic region responses to drugs that were injected intravenously. The branch of the coronary artery was completely occluded in the present study, and therefore no drugs injected intravenously should be distributed to the ischemic region. It is known, however, that myocardial blood flow does not reduce to zero even after complete occlusion of the coronary artery, and that epicardial blood flow is larger than endocardial flow in the ischemic region.\(^21\) Accordingly, it is not surprising to assume that a small amount of the drug injected intravenously would be distributed to the ischemic region and affects myocardial contractile force of the epicardial layers in the ischemic region.

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