AN EXPERIMENTAL STUDY ON THE ROLE OF CORONARY COLLATERAL DEVELOPMENT IN PRESERVATION AND IMPROVEMENT OF CONTRACTILE FORCE IN THE ISCHEMIC MYOCARDIUM

MITSUHIRO YOKOYAMA, TETSUO MIZUTANI, KATSUAKI FUJWARA, TAKAYOSHI AZUMI, HISASHI FUKUZAKI AND TATSUYA TOMOMATSU*

Attempts have been made to demonstrate that the presence of coronary collateral development can preserve and improve the regional contractile force in the ischemic myocardium. Studies were carried out in dogs with developed collaterals and in control dogs.

Contractile force was measured with strain-gauge sutured onto the ischemic and the border areas of the myocardium. After ligation of the anterior descending coronary artery, an augmentation of coronary collateral flow via the left circumflex artery was carried out by means of infusion pump up to two and a half fold level. In dogs with developed collaterals, contractile force decreased by $57.6 \pm 11.1\%$ $(p < 0.01)$ in the ischemic area and $27.2 \pm 5.4\%$ $(p < 0.01)$ in the border area after coronary ligation. The marked recovery of contractile force up to $63.5 \pm 20.4\%$ $(p < 0.05)$ of control level in the ischemic area and $70.4 \pm 20.4\%$ $(p < 0.01)$ in the border area was observed by the augmentation.

In control dogs, however, contractile force decreased by $93.2 \pm 17.2\%$ $(p < 0.01)$ in the ischemic area and $24.6 \pm 5.5\%$ $(p < 0.01)$ in the border area after the ligation. The augmentation of coronary flow did not recover the depressed contractile force in both areas. These results indicated that the beneficial effect was observed only when the ischemic area was supplied by developed collaterals and closely correlated with the extent of coronary collateral development.

IN the presence of coronary atherosclerosis, coronary collaterals may develop and constitute the most important blood supply to the ischemic area of the heart, while coronary collaterals are poor in the normal heart.

Key Words:
- Coronary collateral
- Regional contractile force
- Coronary flow augmentation

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were used in this study. The data reported here were collected from experiments with 10 mongrel dogs subjected to chronic myocardial ischemia (dogs with developed collaterals) and 14 dogs not subjected to prior chronic constriction (control dogs). Dogs with developed collaterals were prepared by placing an aneroid constrictor on the left circumflex coronary artery from four to five weeks prior to the observation. The electrocardiographic examination was done to detect the appearance of abnormal Q wave before the aneroid implantation and the experimental procedures. Dogs with abnormal Q wave were discarded from this study. All animals were anesthetized with sodium pentobarbital, 25 mg/Kg, i.v. Under the ventilation by a mechanical respirator with room air, a left lateral thoracotomy was performed and the fourth to sixth ribs on the left side were removed. The heart was cradled in the pericardium to expose the anterolateral part of the left ventricle. The anterior descending coronary artery about 3 cm distal to its origin and the proximal part of the circumflex artery (or the distal segment of the vessel to the aneroid constrictor in the chronic preparation) were isolated and encircled with silk threads.

In all experiments, anticoagulation was achieved by initial injection of 5000 U heparin and subsequent injection of 1000 U every 30 minutes.

The experimental preparation is shown in Figure 1. Immediately after ligation of the circumflex artery, its distal portion was cannulated and perfused from the left carotid artery through a Havard infusion pump (Model-1210). Aortic blood pressure via a femoral artery catheter and coronary arterial perfusion pressure which was measured through a side arm proximal to the site of cannulation were monitored with electric transducer. The initial coronary flow rate was adjusted so that coronary perfusion pressure was equivalent to or very near the aortic pressure. Aortic flow and coronary flow were measured with a square-wave electromagnetic flow meter (Nihon-Kohden MF-26). Local myocardial contractile force was measured with Walton-Brodie strain-gauge arches with micro-adjustable feet.

One arch was sutured at a depth of approximately 6 mm onto the anterior surface of the left ventricle supplied by the anterior descending artery and expected to be ischemic after its occlusion (ischemic area) in an orientation parallel to the anterior interventricular sulcus.

METHOD

Adult mongrel dogs, weighing 10–19 Kg, correlation between the anatomical extent of collateral channels and the functional indices of the coronary collateral circulation, i.e. peripheral coronary pressure and retrograde flow. The angiographic studies of the effect of the coronary collateral circulation upon the left ventricular function in patients with coronary artery disease were made by many investigators. There are diverse opinions about the role of the coronary collateral circulation in the preservation of regional myocardial contraction in the ischemic heart.

The degree to which these collateral vessels serve to support and maintain the myocardial contraction in the ischemic myocardium has remained uncertain.

The purpose of the present study was to determine whether and to what degree the development of coronary collaterals preserved the contractile force in the ischemic area produced by coronary ligation and improved it by increasing coronary blood flow through the collateral channels.

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TABLE I  SUMMARY OF RESULTS FOLLOWING LIGATION OF THE ANTERIOR DESCENDING CORONARY ARTERY AND SUBSEQUENT CORONARY FLOW AUGMENTATION IN 10 DOGS WITH DEVELOPED COLLATERALS.

<table>
<thead>
<tr>
<th></th>
<th>Before Lig.</th>
<th>After Lig.</th>
<th>Coronary Flow Augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  SE</td>
<td>Mean  SE</td>
<td>X 1.5  Mean  SE</td>
</tr>
<tr>
<td>HR</td>
<td>187 10</td>
<td>189 13</td>
<td>191 12  192 12</td>
</tr>
<tr>
<td>mAP</td>
<td>81.4 6.3</td>
<td>71.9## 5.8</td>
<td>73.7 5.1  73.4 5.5</td>
</tr>
<tr>
<td>AF</td>
<td>2.09 0.16</td>
<td>1.67## 0.14</td>
<td>1.71 0.14  1.77 0.18</td>
</tr>
<tr>
<td>CW</td>
<td>175 22</td>
<td>124## 15</td>
<td>128 15  134* 16</td>
</tr>
<tr>
<td>mPP</td>
<td>88.6 6.8</td>
<td>73.5## 4.4</td>
<td>100.5** 4.4  122.0** 5.4</td>
</tr>
<tr>
<td>mPCP</td>
<td>28.8 3.4</td>
<td>36.6* 5.5</td>
<td>44.1** 7.1  51.6## 9.2</td>
</tr>
</tbody>
</table>

Results expressed are mean ± SE.
# , ##=Significantly different from preligation control p<0.05, and p<0.01. *, ** significantly different from post ligation values at p<0.05, and p<0.01.
C.Lig=coronary ligation, HR=heart-rate, mAP=mean aortic pressure, AF=aortic flow, CW=cardiac work, mPP=mean coronary perfusion pressure. mPCP=mean peripheral coronary pressure.

TABLE II  SUMMARY OF RESULTS FOLLOWING LIGATION OF THE ANTERIOR DESCENDING CORONARY ARTERY AND SUBSEQUENT CORONARY FLOW AUGMENTATION IN 14 CONTROL DOGS. ABBREVIATIONS AS IN TABLE I.

<table>
<thead>
<tr>
<th></th>
<th>Before Lig.</th>
<th>After Lig.</th>
<th>Coronary Flow Augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean  SE</td>
<td>Mean  SE</td>
<td>X 1.5  Mean  SE</td>
</tr>
<tr>
<td>HR</td>
<td>170 7</td>
<td>168 7</td>
<td>165 7  165 8</td>
</tr>
<tr>
<td>mAP</td>
<td>82.9 3.2</td>
<td>73.9## 3.5</td>
<td>74.1 3.4  72.5 3.1</td>
</tr>
<tr>
<td>AF</td>
<td>2.02 0.15</td>
<td>1.58## 0.13</td>
<td>1.65 0.14  1.64 0.13</td>
</tr>
<tr>
<td>CW</td>
<td>170 18</td>
<td>121## 14</td>
<td>125 15  122 14</td>
</tr>
<tr>
<td>mPP</td>
<td>90.6 4.6</td>
<td>81.4# 5.1</td>
<td>127.2** 8.3  147.7** 8.8</td>
</tr>
<tr>
<td>mPCP</td>
<td>16.3 1.8</td>
<td>17.8* 1.8</td>
<td>18.6** 1.8  18.8** 1.9</td>
</tr>
</tbody>
</table>

The other strain-gauge arch was sutured in the same fashion onto the border area which was determined by epicardial vascular architecture. In each case, the arch was extended by a microscrew so that the subtended muscle segment was stretched by 20% of its initial length. The responsiveness of the gauges to transient occlusion of the anterior descending artery was examined before permanent ligation.

The term "contractile force" was chosen to describe the developed tension during systole. Negative deflection of the recording during systole was defined as "systolic bulge" and expressed by "minus" notation. After stabilization of all hemodynamic parameters, the anterior descending artery was ligated. A polyethylene cannula with 2 mm internal diameter was introduced into the artery beyond the point of ligation and connected to a pressure transducer. This procedure was used for the measurement of peripheral coronary pressure in the anterior descending arterial bed. The parameters mentioned above were recorded as post infarction values at 15 min after coronary ligation. Thereafter, the coronary flow rate was increased in a stepwise manner with infusion pump from the post infarction level to two and a half fold at every 3 min interval (coronary flow augmenta-
coronary arterial perfusion and prolonged anesthesia.

Changes in contractile force in ischemic and border areas after the ligation were analysed by percent changes from pre-ligation (control) level. In addition, the degree to which the affected myocardium recovered its contractile force during the flow augmentation was estimated by a recovery rate (%), \( b - c / b - a \times 100 \). “a” and “b” are the values of contractile force prior to and at 15 min after coronary ligation, respectively and “c” denotes the value obtained by coronary flow augmentation. The rate of increase in peripheral coronary pressure during the augmentation was calculated by dividing the difference of the values before and during the flow augmentation by post-ligation value. Results are expressed as mean ± standard error and the significance of difference between the means was determined by Student’s t-test. Difference with \( p < 0.05 \) is regarded as statistically significant.

After completion of the experimental studies, the animals were sacrificed and the hearts were removed. The circumflex branch was cannulated and a barium-gelatine mixture was injected with Schlesinger’s method to delineate the area of the distribution of the left coronary artery and the existence of collaterals.

RESULTS

Effect of coronary ligation.

The effect of coronary ligation on systemic and coronary hemodynamics was summarized in Table I and II. In dogs with developed collaterals (Table I), heart-rate was not changed and mean aortic pressure decreased by 10.9 ± 3.2% (\( p < 0.01 \)), aortic flow by 20.1 ± 2.4% (\( p < 0.01 \)) and cardiac work by 28.8 ± 3.2% (\( p < 0.01 \)) after coronary ligation. Coronary perfusion pressure was reduced by 16.2 ± 4.4% (\( p < 0.01 \)) and mean peripheral coronary pressure was 28.8 ± 3.4 mmHg. In control dogs (Table II), coronary ligation did not change heart-rate, but decreased mean aortic pressure by 10.4 ± 2.1% (\( p < 0.01 \)), aortic flow by 28.9 ± 2.9% (\( p < 0.01 \)) and cardiac work by 28.9 ± 2.9% (\( p < 0.01 \)). Coronary perfusion pressure decreased by 10.0 ± 3.4% (\( p < 0.05 \)). Mean peripheral coronary pressure was 16.3 ± 1.8 mmHg and never exceeded 30 mmHg.

The degree of systemic hemodynamic changes after coronary ligation was not significantly different in both groups of dog (\( p > 0.05 \)), while
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peripheral coronary pressure was significantly higher in dogs with developed collaterals than in control dogs (p < 0.01).

The effect of coronary ligation on local myocardial contractile force was shown in Fig. 2 and 3. Systolic bulge was recorded in the ischemic area in one of 10 dogs with developed collaterals and in 5 of 14 control dogs. In dogs with developed collaterals, coronary ligation decreased contractile force by 57.6 ± 11.1% (p < 0.01) in the ischemic area and 27.2 ± 5.4% (p < 0.01) in the border area. In control dogs, the contractile force was reduced by 93.2 ± 17.2% (p < 0.01) in the ischemic area and 24.6 ± 5.5% (p < 0.01) in the border area.

**Effect of coronary flow augmentation.**

The effect of coronary flow augmentation on systemic and coronary hemodynamics was summarized in Table I and II. In dogs with developed collaterals (Table I), coronary perfusion pressure showed stepwise and significant increase up to 192.3 ± 12.9% (p < 0.01) by graded coronary flow augmentation. Mean peripheral coronary pressure increased up to 172.9 ± 16.5% (p < 0.01) and in three dogs it exceeded more than 50 mmHg. The coronary flow augmentation resulted in the least change in heart-rate and mean aortic pressure and a little, but significant increase in aortic flow (9.0 ± 2.8%, p < 0.05) and cardiac work (11.2 ± 3.5%, p < 0.05).

In control dogs (Table II), coronary perfusion pressure showed stepwise increase up to 202.1 ± 11.8% (p < 0.01) during the augmentation. Progressive increase in coronary flow resulted in a small increase in peripheral coronary pressure up to 117.4 ± 4.3% (p < 0.01). No significant changes were found in heart-rate, mean aortic pressure, aortic flow and cardiac work.

The effect of coronary flow augmentation of local myocardial contractile force was shown in Fig. 2 and 3. In dogs with developed collaterals, contractile force was recovered by 63.5 ± 20.2% (p < 0.01) in the ischemic area and 70.4 ± 20.4% (p < 0.01) in the border area by the augmentation. There was a negative correlation between the reduction rate of contractile force in the ischemic area after the ligation and the post infarction value of mean peripheral coronary pressure/mean perfusion pressure (r = 0.75, p < 0.01) (Fig. 4). In addition, a significant linear correlation was found between the recovery rate of contractile force in the ischemic area and the increase in peripheral coronary pressure during the augmentation (r = 0.78, p < 0.01) as shown in

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*Fig. 4. Correlation between reduction in contractile force in the ischemic area by coronary ligation and post-ligation value of mean peripheral coronary pressure/mean coronary perfusion pressure. CF=contractile force, m-PCP=mean peripheral coronary pressure, m-PP=mean coronary perfusion pressure.*

*Fig. 5. Correlation between recovery rate of contractile force in the ischemic area and the increase of peripheral coronary pressure by coronary flow augmentation in dogs with developed collaterals. CF=contractile force, m-PCP=mean peripheral coronary pressure.*
Fig. 5.

In contrast, the contractile force was not recovered both in the ischemic and the border areas of control dogs by the coronary flow augmentation.

After the maximal augmentation was attained, coronary flow was reduced in the same manner in both groups of dog. Despite the decrease in coronary flow, the contractile force in the ischemic and the border areas remained to be improved in dogs with developed collaterals (Fig. 2 and 3).

After the experimental procedures, the absence of myocardial scar in areas subjected to chronic constriction was confirmed macroscopically.

Postmortem coronary angiogram in control heart hardly opacified the anterior descending artery through minimal collateral channels from the circumflex artery into which the contrast material was injected. On the contrary, in heart with developed collaterals, many intercoronary communications were present between the circumflex and the anterior descending bronches and the contrast material passed readily from the circumflex to the anterior descending artery.

DISCUSSION

This investigation has demonstrated that the presence of developed collateral vessels was able to preserve the contractile force during ischemia and a selective increase in coronary perfusion was able to improve contraction abnormalities in the ischemic area. In this study the development of collateral channels between the left anterior descending artery and the circumflex artery was achieved by the gradual obstruction of the left circumflex artery by applying an ameroid constrictor for 4–5 weeks. Peripheral coronary pressure was used as an index of the development of the coronary collateral circulation. The measurement of peripheral coronary pressure showed a significantly higher value in dogs with developed collaterals than in control dogs before and during the coronary flow augmentation. It was interpreted that large collateral channels have developed in chronic ischemic dogs and consequently abundant blood flow could be supplied to the ischemic area through them. The postmortem coronary angiographic studies gave the evidence to support this interpretation.

Many experimental studies have been done to examine the influence of coronary collateral development on regional distribution of myocardial blood flow; ventricular fibrillation threshold and survival rate after coronary ligation. However, its effect on myocardial contraction during acute ischemia has not yet been studied thoroughly, while a part of this study was reported previously.

The pathophysiological role of coronary collateral circulation in patients with obstructive coronary artery disease is still controversial. Some authors have reported that collaterals have beneficial effects on cardiac function and prognosis in patients with coronary artery disease. Other authors, however, have the opinions that the presence of collaterals neither protects the myocardium from deterioration of contraction nor improves the prognosis.

This disagreement appears to be caused by 1) difficulties to get enough informations about collateral flow and regional myocardial collateral state in man, 2) inhomogeneous group of patients including the various severities of the obstructive lesions.

The contractile characteristics of ischemic myocardium have been the subject of study since 1935 when Tennant and Wigger first showed systolic expansion of an ischemic segment of myocardium following coronary artery ligation. Several observers have generally reported the expected decrease in contractile force while others have reported inversion of the contractile force (systolic bulge). This phenomenon of systolic bulge in the ischemic myocardium was observed more frequently in control dogs than in dogs with developed collaterals after coronary ligation. The magnitude of reduction in contractile force in control dogs was greater than in dogs with developed collaterals. Despite the markedly different response of regional myocardial contraction after the ligation, systemic hemodynamic parameters showed no significant difference between dogs with and without collaterals. This is partly due to the small ischemic area produced by ligating the anterior descending coronary artery and also due to the rather shorter duration of applying the ameroic constrictor for the full development of collaterals.

It has been reported that the depressed contractile force in the ischemic and the border areas was not restored for 90 min in dogs not subjected to chronic ischemia.

In addition, coronary flow augmentation did not restore the depressed myocardial contractile force in the ischemic and the border areas of control dogs.
This implies that the functional capacity of the coronary collateral circulation in the control dog is not sufficient to improve and restore the depressed contraction in the ischemic area. On the contrary, the results observed in dogs with developed collaterals clearly indicated that the presence of developed collaterals could preserve myocardial contractile force in the ischemic area and also could improve it in the ischemic and the border areas by the coronary flow augmentation. However, it is well known that there is a significant difficulty in comparing the collateral system in dog with that in human, because dog has larger and more numerous collaterals than human. In addition, it is also reported that there was marked distributional difference of the collaterals between human and dog. The degree to which the adjustment takes place through the collateral circulation might be different between them, but a recent study in patients with total occlusion of the left main coronary artery revealed that a well-developed collateral circulation was associated with preservation of left ventricular contractility.

This report strongly suggests that some beneficial effects of collaterals on myocardial function could be expected also in the ischemic myocardium of human.

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