DEVELOPMENT OF CORONARY COLLATERAL CIRCULATION IN MINIATURE SWINE AND EFFECTS OF SEVERAL DRUGS*. 
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Abstract—To determine whether or not the development of collateral channels can be accelerated by administration of vasodilators and whether the opening up of functional collateral channels is associated with an improved survival rate, a gradual occlusion of the major branches of the left coronary artery was produced in miniature swine with an Ameroid constrictor. Oral administration of drugs (twice a day) was started seven days before operation and was continued throughout the experimental period of 2 months. While the survival rate of the untreated animals was 6/15 (40%), survival rates of animals treated with adenosine potentiators, dipyridamole and dilazep were 4/7 (57.1%), and 5/7 (71.4%), respectively. However, a significant improvement of the survival rate was attained by KI 2119; survival rate was 6/7 (85.7%). Coronary angiography of the survived control animals revealed numerous, fine, collateral communications between the left and right coronary arteries. Treatment with dipyridamole and dilazep resulted in formation of a dense network of thick collaterals. To quantify the degree of formation of the collateral channels, the anatomic anastomotic indices (AAI's) were calculated using histological specimens of the anterior free wall of the left ventricle. According to Menick et al. (16), AAI is a good measure of the functional capacity of the collateral vessels. AAI's of the animals treated with dipyridamole and dilazep were 2416.6±454.0 and 1864.7±248.3 as compared with 704.3±407.9 of the untreated animals. AAI's of the KI 2119-treated animals did not differ from those of the control animals. A linear correlation was observed between the survival rate and AAI's (r=0.74, p<0.05), indicating a close relationship between the survival rate and the development of functional collateral channels.

It is generally accepted that well-developed and functional collateral arteries provide an effective defence against obstructive diseases of the coronary arteries. Although collaterals have been found in normal hearts of man (1-5), dog (6-8) and pigs (9-10), the functional capacity of these anastomoses is not sufficiently great to protect the heart from infarcts or ventricular fibrillation resulting from a sudden occlusion of the main trunks of the coronary arteries. For the collaterals to function as an efficient defence, a prior enlargement and growth of the pre-existing vessels is necessary, and such is effected by arterial hypoxia, anemia, and stenosis and occlusion of the coronary arteries. In addition, several

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coronary vasodilators have been shown to promote such a transformation in the dog. However, certain fundamental differences exist in coronary arteries between the dog and the human: Arrangements of coronary artery of the dog are strikingly different from that of humans (11-12), and many functional collateral channels are present even in the normal myocardium in the dog. By contrast, the pig fulfills most requirements of similarity. The course of the coronary arteries is essentially similar to that found in 85 to 90 percent of humans and intercoronary anastomoses were minimal in the normal heart. If intercoronary connections do exist, they are found only at the capillary level and are less than 20 μ in diameter. In view of these situations, the pig was selected as the experimental animal and gradual narrowing to occlusion of the major branches of the left coronary artery was produced with an Ameroid constrictor to determine whether the development of the collateral channels could be accelerated by administration of vasodilators and whether the opening up of functionally-adequate collateral channels was indeed associated with the survival of the animal.

MATERIALS AND METHODS

Miniature pigs (Pitman-Moore strain) of either sex weighing between 32 and 80 kg (5–10 months of age) obtained from Nippon Institute for Biological Science (NIBS) were anesthetized with halothane inhalation (8% in 95% O₂ + 5% CO₂) after premedication with ketamine (10 mg/kg s.c.) and atropine (40 μg/kg i.m.). An airway was established by means of an endotracheal tube (7 mm) and animals were artificially ventilated with positive pressure inflation using a respirator (Takashima Shoten). After shaving and routine skin aseptic preparation with chlorhexizine, the thorax was opened in the third left intercostal space. The left coronary artery was approached with retraction of the left atrial appendage after opening of the pericardium. The first part of the anterior descending branch of the left coronary artery was then carefully dissected free from connective tissue and fat for a distance of at least 1.5 cm, and cylindrical constrictor of a hygroscopic casein base plastic (Ameroid) (13) was slipped onto the exposed artery 5 mm from its ostium to produce a gradual occlusion. The constrictors were 6.0 mm in diameter and 4.0 mm long, and encased in a

![Fig. 1. The dimensions of the Ameroid constrictor used for production of gradual occlusion of the coronary artery. Hygroscopic casein base plastic (Ameroid) is encased in a stainless steel cuff.](image-url)
stainless steel cuff to ensure constriction as shown in Fig. 1. Eccentric lumens measuring 1.9 mm diameter were precision drilled and entered by slits 1.0 mm wide. The constrictors were kept in a desiccator until their use at operation. After application of the constrictors, the chest was closed in layers. When normal respiration was resumed, the animals were returned to their cages. Standard lead II electrocardiograms were observed continuously during the operation. During the next three days, the animals were given 200,000 l.U. penicillin and 0.25 g of streptomycin, intramuscularly. The experimental period was set for 2 months. On the basis of the lifespan, one month in the pig is assessed to be equivalent to 6.5 months in the human (14). Therefore, the experimental period of 2 months chosen in the present experiments corresponds to 13 months of the human. When animals died or were sacrificed after the lapse of 2 months, the right coronary artery and the circumflex branch of the left coronary artery were perfused with isotonic saline at a pressure of 40-50 mmHg until clear fluid flowed from the coronary sinus. Perfusion with a radiopaque material then followed. A mixture of 8%, gelatin and 40%, BaSO₄ was prepared and perfused at a temperature of 38°C under a pressure of 100 mmHg for 5 min. The heart was placed in a bowl of ice flakes until the injectate gelled. Radiographs were then taken after the heart has been opened "like a book" and laid flat ("unrolling" of the heart), following the procedure of Schoenmacker (15), and were studied for the presence of collateral channels with low power X-ray generation (Softex EM). By means of this method, fine branches of the arteries were filled, but no venous filling was observed. Therefore, any collateral channels which were demonstrated were considered to be arterio-arterial. Thereafter, blocks for histological study were taken. After routine histological processing, 4 μ paraffin sections were prepared and stained with hematoxylin and eosin and with Weigert's elastica Van Gieson.

The estimation of functional collateral flow capacity from postmortem injection specimens has been a persistent problem in studies of coronary collateral circulation. Recently Menick et al. (16) proposed an anatomic anastomotic index which correlated well with the collateral vascular capacity defined as dividing retrograde flow by diastolic aortic blood pressure.

Based on Poiseuille's law, which states: volume of flow = \( \frac{Pr^4}{8\mu L} \) where \( P \) = pressure gradient, \( r \) = radius, \( \mu \) = viscosity of blood, and \( L \) = axial length of the vessel, the anatomic anastomotic index (AAI) is calculated as the sum of the fourth power of the radius times the number of collaterals and simplified by dividing by 10⁶. In view of the subendocardial and endomural localization of the collaterals in the swine, calculation of AAI's was conducted using the histological specimens (stained with hematoxylin and eosin) of the anterior free wall of the left ventricle. From a representative specimen taken from the marginal regions of the infarction as judged by gross inspection (Collaterals developed mainly in the borderzone between anoxic and supposedly normally perfused myocardium), eight fields of vision (1.5 x 1.2 mm) were selected for evaluation of the collateral formation. All sections were cut perpendicular to the longitudinal axis of the vessel to ensure unbiased measurement of
vascular dimensions. Tangentially cut sections were omitted. The internal diameters and the numbers were recorded and the vessels were separated into the following four groups, according to their size:

- Group I 12–49 μ
- Group II 50–99 μ
- Group III 100–149 μ
- Group IV >150 μ

AAI's were calculated using the fourth power of the mean radius of each group instead of the fourth power of the radii of the individual vessels. Since there are practically no collateral vessels in the normal swine myocardium, all the vessels filled with radioopaque materials were taken to be newly-formed collaterals.

Drugs used were: Isosorbide dinitrate (Eisai), dipyridamole (Boehringer), dilazep (Kowa), prenylamine (Hoechst), N,N'-bis-[3,3-diphenyl-propyl-(1)]-ethylenediamine dihydrochloride (K1 2119) (Kantoishi), diltiazem (Tanabe), diazepam (Chugai) and bupranolol (Kaken Kagaku). These drugs were administered orally for 6 days before the operation and thereafter until the death of the animal. Doses of the drugs were determined on the basis of the average human dosage, if such are available, with reference to the fact that the ratio of animal/human dose approaches unity when calculated on a surface area basis (17). Body surface area can be estimated as: 0.1 × (Body weight)$^\frac{2}{3}$ (18).

Comparison of the histopathologic changes of the myocardium was not conducted, since it was considered impossible to make an accurate assessment of these changes in a quantitative manner. Gross observations of infarct size were very inaccurate. Over-all measurement of area has little value, because histologic evidence of ischemic necrosis can be found outside the limits of gross abnormality.

**RESULTS**

*Degree of constriction of the Ameroid constrictor*

When placed in the body, the Ameroid constrictors absorbed fluid and, as the steel cuff prevented expansion, they slowly constricted into the central lumen. The slit closed

![Fig. 2. The daily reduction of the diameter of lumens of Ameroid constrictors. Abscissa: days after the application of the constrictors. Ordinate: diameters of the lumen in Ameroid still open. The horizontal dotted line is drawn at a lumen diameter of 1.34 mm, which corresponds to a reduction of 50% of the lumen.](image-url)
first. Fig. 2 illustrates the degree of patency of the lumens of the Ameroid constrictor at a time when the animals died. As is evident from this figure, the cross-sectional area of the lumen became less than 50% of the initial size 7–10 days after the implantation of the constrictor. Incidence of deaths of the control animals occurred predominantly around this period, in agreement with the original findings of Vineberg et al. (19).

**Rate of survivors**

In 19 animals, the anterior descending branch of the left coronary artery was occluded with a constrictor without administration of any drugs. Of these, 13 died and 6 survived; 4 died in less than 24 hours; and 9 died between 2–13 days (Table 1). In order to obtain information on changes occurring within the myocardium, the activities of the several key enzymes in the blood were determined. Blood samples were withdrawn from the ear vein and allowed to clot to obtain serum. Chemical analyses were performed using a rapid blood analyzer system (Kyoto Kagaku RaBA-3010). Blood chemistry values of the miniature pig before the operation were listed in Table 2. Fig. 3 depicts a representative record

| Table 1. Effects of drugs on the survival rate. Survival rate was calculated excluding the deaths which occurred between 0 and 1 day after operation. Probabilities were calculated by exact Fischer method |
| --- |
| **Drugs** | **Doses (mg/kg/day)** | **n** | **Death (days)** | **Survivors** | **Survival rate (%)** | **Probabilities** |
| **Control** | 4 | 0–1 | 9 | 6 | 6/15 (40.0) | |
| Isosorbidedinitrate | 3 | 0 | 3 | 1 | 4 | 4/8 (50.0) | 0.49 |
| Dipyridamole | 10 | 7 | 0 | 2 | 4 | 4/7 (57.1) | 0.38 |
| Dilazep | 3 | 6 | 1 | 2 | 2 | 2/5 (40.0) | 0.70 |
| Dilazep | 20 | 8 | 1 | 2 | 5 | 5/7 (71.4) | 0.18 |
| Dilazep (post ope.) | 20 | 5 | 0 | 1 | 3 | 3/5 (60.0) | 0.40 |
| Prenylamine | 10 | 7 | 2 | 3 | 2 | 2/5 (40.0) | 0.70 |
| KI 2119 | 3 | 10 | 3 | 0 | 6 | 6/7 (85.7) | 0.06 |
| KI 2119 | 30 | 5 | 0 | 2 | 3 | 3/5 (60.0) | 0.40 |
| Diltiazem | 10 | 7 | 2 | 3 | 2 | 2/5 (40.0) | 0.70 |
| Diazepam | 5 | 5 | 1 | 0 | 2 | 2/4 (50.0) | 0.57 |
| Buprananolol | 5 | 6 | 1 | 1 | 2 | 2 | 2/5 (40.0) | 0.70 |

| Table 2. Blood chemistry of the miniature swine used in this experiment |
| --- |
| **GOT** | Karmen U | **GPT** | Karmen U | **LDH** | Wroblewski U | **Albumin** | g/dl | **Glucose** | mg/dl | **ALP** | K.A.U. | **Cholesterol** | mg/dl | **Total protein** | g/dl |
| n = 23 | | | | | | | | | | | | | | |
| | 41.4 ± 2.8 | 30.5 ± 2.6 | 1452.3 ± 92.7 | 2.7 ± 0.1 | 80.0 ± 4.0 | 12.7 ± 1.3 | 85.2 ± 3.1 | 7.3 ± 0.1 |

GOT: glutamic-oxaloacetic transaminase. GPT: glutamic-pyruvic transaminase. LDH: lactic dehydrogenase. ALP: alkaline phosphatase.
of changes in the blood chemistry after implantation of the constrictor. A sharp rise of the activities of creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and glutamic oxaloacetic transaminase (GOT) was first observed a few days after the operation and declined to the control level in about one week. This may be taken to represent a response of the animal to operative intervention and the deaths occurring around this time were omitted in calculation of the mortality as non-coronary deaths. A second rise indicating the occurrence of myocardial infarction then followed and attained a peak at about 10 days. The majority of the animal died at this stage. Usually death occurred suddenly. We witnessed death of the animals several times and such occurred during excitement or after a meal. In 3 instances, the pigs died while the ECG was being recorded. Autopsies revealed acute cardiac failure as the cause of death, and there were no abnormalities other than those in the heart. The heart weight: body weight ratio was 0.46±0.01% (n=28) as compared with 0.39±0.01% (n=14) in control animals (p<0.005). The survival rate of the control animals and animals treated with various drugs are listed in Table 1. The survival rate of the untreated animals was 6/15 (40%). Oral administration of adenosine potentiators, dipyridamole and dilazep, resulted in higher survival rates: 4/7 (57.1%) for dipyridamole and 5/7 (71.4%) for dilazep. Longer survival after gradual coronary occlusion developing over several days was reported in pigs treated with dipyridamole (20). Besides adenosine potentiators, KI 2119 was the only compound that produced a higher survival rate (6/7, 85.7%).

Since the number of experimental animals used was relatively small, the common $X^2$ test was not used for statistical evaluation. Instead, the so-called “exact Fischer test” was
used. For example, in the case of KI 2119, the following 4-panel table was constructed using the survival rate listed in the table.

|        | Survived | Died | Sum |
|--------|----------|------|-----|
| Control | 6 (a)    | 9 (c) | 15  |
| KI 2119 | 6 (b)    | 1 (d) | 7   |
| Sum     | 12       | 10   | 22  |

With the marginal totals unchanged, a more extreme occurrence would be:

|        | Survived | Died | Sum |
|--------|----------|------|-----|
| Control | 5        | 10   | 15  |
| KI 2119 | 7        | 0    | 7   |
| Sum     | 12       | 10   | 22  |

The probabilities are calculated recursively using the following equation (21):

\[
P_{i+1} = \frac{a_i \cdot d_i}{b_{i+1} \cdot c_{i+1}} \cdot P_i
\]

\[P_i\] is calculated from

\[
P_1 = \frac{15! \cdot 12! \cdot 10!}{22!} \cdot \frac{1}{6! \cdot 6! \cdot 9! \cdot 1!} = 0.0542
\]

\[
P_2 = \frac{6 \cdot 1}{7 \cdot 10} \cdot 0.0542 = 0.0046
\]

\[P = P_1 + P_2 = 0.0588
\]

Therefore, if the hypothesis of proportionality is true, the probability of observations of the kind recorded would be around 6\%. The probabilities of the set of survival rate observed for other drugs are listed in Table 1. On gross examination of the heart, myocardial infarction was noted in most of the animals. Although the size of the infarcted area was variable, such were mostly transmural and occupied the anterior wall of the left ventricle and the parts of the interventricular septum. There was considerable thinning of the left ventricular wall in the region of the infarct.

**Effects of drugs on the collateral formation**

As shown in Fig. 4, post-mortem coronary angiography revealed only a faint shadow in the major branches of the anterior descending branch of the left coronary artery of the animals which died soon after the operation. By contrast, when animals survived the planned experimental period with occluded coronary arteries, numerous, fine, collateral communications were detected between the anterior descending branch of the left coronary
FIG. 4. Coronary angiograms of untreated animals. Upper panel: coronary angiogram of the animal which died within 24 hr after the operation. Lower panel: coronary angiogram of the control animals survived coronary artery occlusion produced by Ameroid constrictor for two months. An emulsion of 40% BaSO₄ and 8% gelatin was injected into right and left circumflex coronary arteries.

FIG. 5. Coronary angiogram of the animal treated orally with dilazep (20 mg/kg/day)
TABLE 3. Anatomic anastomotic indices (AAI’s) of the animals which survived gradual occlusion of the coronary artery for two months.
For details see text.

| Drugs          | mg/kg/day | n  | 12-49um | 50-99um | 100-149um | >150um | Survivor’s AAI |
|---------------|-----------|----|----------|----------|-----------|---------|----------------|
| Control       |           |    | 335.6 ± 71.7*  | 24.0 ± 4.1 | 6.0 ± 0.8 | 3.2 ± 1.3 | 704.3 ± 407.9 |
| Isosorbidedinitrate | 3         | 4  | 331.1 ± 101.2 | 42.0 ± 14.4 | 8.5 ± 2.3 | 5.0 ± 0.7 | 914.1 ± 286.6 |
| Dipyridamole   | 10        | 4  | 417.0 ± 76.9  | 20.5 ± 1.2 | 5.5 ± 0.9 | 8.5 ± 1.9 | 2416.6 ± 454.0* |
| Dilazep        | 3         | 2  | 287.0       | 33.5      | 9.5       | 9.5       | 1117.8 ± 70.2 |
| Dilazep        | 20        | 5  | 319.8 ± 95.8  | 20.2 ± 2.4 | 6.4 ± 1.5 | 6.6 ± 1.5 | 1864.7 ± 248.3* |
| Dilazep (post op.) | 20      | 2  | 276.0       | 30.5      | 11.5      | 4.0       | 541.2 ± 112.4 |
| Prenylamine    | 10        | 2  | 367.0       | 23.0      | 2.5       | 3.0       | 735.8 ± 470.8 |
| KI 2119        | 3         | 5  | 406.4 ± 45.1  | 43.2 ± 8.1 | 9.0 ± 3.1 | 4.6 ± 1.2 | 683.2 ± 154.4 |
| KI 2119        | 30        | 3  | 586.7 ± 101.4 | 33.0 ± 3.5 | 6.7 ± 2.2 | 4.7 ± 1.5 | 891.6 ± 289.2 |
| Diltiazem      | 10        | 2  | 294.0       | 19.0      | 7.5       | 2.5       | 527.8 ± 456.1 |
| Diazepam       | 5         | 2  | 397.0       | 13.5      | 5.5       | 5.0       | 791.8 ± 700.0 |
| Bupranolol     | 5         | 2  | 281.5       | 20.5      | 9.5       | 6.5       | 1052.3 ± 267.0 |

*P < 0.05  †Mean numbers of collateral vessels of these diameters
artery and right coronary artery. Collaterals are located mainly endocardially and endomurally and especially in structures with a dual blood supply, i.e. the interventricular septum and anterior papillary muscle. Treatment with dipyridamole and dilazep resulted in formation of a dense network of thick collaterals (Fig. 5), while there was practically no difference in the collateral development between the control animals which survived and the animals treated with other drugs.

To assess the functional collateral flow capacity, the anatomic anastomotic indices (AAI's) of survivors were calculated as described in the Materials and Methods section. As shown in Table 3, AAI's were significantly higher in animals treated with dipyridamole and dilazep than in the control (P<0.05).

Relation between survival rate and AAI's

When the survival rate was plotted against the AAI's a linear correlation was observed (r = 0.74, p = 0.05), indicating a close relationship between survival and the establishment of functional collateral channels (Fig. 6). The AAI for KI 2119 was omitted as it belonged to a different population.

DISCUSSION

Kanaya (22) analyzed the time course of collateral formation after ligation of the anterior descending branch of the left coronary artery of the dog. According to his experimental results, the number of anastomotic vessels increased around one week after the
operation and attained peak values 5 weeks after the operation. Thereafter, the total number of collaterals decreased despite the ever-continuing increase in the number of collaterals of intermediate and large size, because the collaterals of small size, which comprised the most abundant group of all, were diminished around this time, indicating that the transformation of the smaller vessels to larger ones was progressing. Although large collaterals were not so numerous as the smaller ones, they were directed toward the periphery of the occluded arteries, suggesting the importance of these type of vessels in protecting the heart from fatal consequences. This evolution has also been demonstrated in the human heart (4). From the point of view of haemodynamic economy this evolution is desirable—the energy spent by the blood flowing through many narrow tubes is much higher than that of the same flow through few wide tubes. Schaper (23) also demonstrated that the newly developed collaterals were thin-walled, rather fragile vessels lacking smooth muscle coat, but transformed themselves in the course of time to normal vessels with layers of smooth muscle. These findings indicate that although collaterals develop relatively early after the induction of infarcts, the vessels, which appeared first, were small and functionally incompetent. It is after transformation to larger fully-matured ones, these vessels function. This view is in agreement with the finding that retrograde flow from the distal end of the occluded artery became sufficiently large only after the lapse of several weeks to several months. Although the anatomical situation is not the same in swine and dogs, the process of the vascular transformation is reported to be quite comparable (24). In contrast to the control animals, animals treated with dipyridamole and dilazep were equipped with large, sturdy anastomoses. Anatomic anastomotic indices calculated as a measure of the functional capacity of these vessels were 2416.6 for dipyridamole and 1864.7 for dilazep, significantly different from 704.3 of the control animals. It seems that dipyridamole and dilazep promoted the transformation of the minute collateral vessels into thicker ones. The pharmacological property common to these two vasodilators is a potentiation of the actions of adenosine. Since hypoxia is assumed to be one of the strongest stimuli for promotion of development of collateral vessels (for references see (4)) and adenosine is a putative mediator of the hypoxic dilatation of the coronary vasculature, it is probable that these two vasodilators accelerated the collateral formation through potentiation of adenosine action. According to Schaper (25) tangential wall tension may play a key role in the vascular transformation and the wall tension can only increase in the presence of a dilatatory stimulus and in the presence of increased or unchanged intravascular pressure. It seems likely that increased vessel wall stress resulting from repeated vasodilatation is the stimulus to growth.

As to the efficacy of the collateral circulation in protecting the heart from fatal consequences, there is still some controversy: There are researchers who contend that the presence or absence of the intercoronary collateral vessels does not alter significantly the incidence of angina, myocardial infarction, and hemodynamic or ventriculographic abnormalities (26–28), while numerous investigations suggest that the development of an adequate bypass blood supply has a significant effect on the condition of the myocardium after vascular occlusion (29–32), especially when the parent arteries from which the col-
laterals originate are healthy (33). Present experiments conducted in the miniature swine clearly demonstrated an excellent correlation between the functional capacity of the collateral vessels and the survival rate.

Lumb and Hardy (34) reported that pentaerythritol tetranitrate produced a significant improvement of mortality of the swine. However, since the occlusion of the coronary artery was completed within 48 hours in their experiments, acute effects of the drug, e.g. the dilatation of the large coronary artery may have caused a better survival rate of the treated-group. None of their arteriograms showed collateral vessels in excess of those sometimes seen in untreated animals. By contrast in our experiments, a complete occlusion occurred only after 7-10 days.

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