Basic Research in
Cardiology

Basic Res Cardiol 84:524–535 (1989)

Microvascular and collateral adaptation in swine hearts following progressive coronary artery stenosis*)

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Summary: We chronically implanted hygroscopic occluders around the left circumflex coronary artery in 49 anesthetized young male domestic pigs and we studied the development of a collateral circulation at 4, 8, 12, and 26 weeks after implantation. At these time intervals groups of animals were again anesthetized, the hearts were explanted and perfused in Langendorff-fashion with leucocyte-filtered pig blood. Maximal coronary vasodilation was induced with adenosine and global (electromagnetic), and regional (tracer microspheres) blood flow was measured at 40, 60, 80, and 100 mm Hg of perfusion pressure. At 4 weeks after occluder implantation maximal left circumflex collateral blood flow was about 20 % of normal maximal flow. Collateral flow rose to 60 % of maximal normal flow between 4 and 8 weeks and did not improve further with longer time intervals.

In contrast to the canine heart numerous small vessels develop in response to ischemia in the pig heart. These vessels develop throughout the entire risk region with a slight preference for the subendocardium. They appear on tomographic angiograms as a dense "blush". The study of the relationship between peripheral coronary pressure vs collateral flow showed a relationship much steeper than that of normal maximal flow vs aortic perfusion pressure which indicates that the minimal resistance of the risk region was decreased as part of the mechanism to ensure adequate blood supply in a situation of progressive coronary narrowing.

Key words: angiogenesis, collateral circulation, swine heart, coronary stenosis, myocardial infarction

Introduction

Quantitative data that have been reported on the development of a collateral circulation following progressive coronary artery stenosis in the canine heart may not be entirely representative for all aspects of vascular adaptation in the human heart (1–4). For example (5), the canine heart can rely on more collateral blood flow after acute coronary occlusion than can either the human or the porcine heart, consequently its chances of survival may be better. For these reasons the search for a better model of progressing human coronary artery disease continues. We were interested in the quantitative aspects of collateral development in the swine heart because of the well-known anatomical and metabolic similarities with the human heart (6–8). The present study is focused on quantitative pressure-flow relationships as a function of time, on the mechanisms of vascular adaptation in the pig heart, and on differences with the canine model. This report suggests that the high collateral resistance in the porcine heart is partially compensated for by a fall of the minimal microvascular resistance through vascular growth in the entire recipient bed.

*) The results of this project were presented at the 60th Scientific Sessions of the American Heart Association, November 1987, Anaheim, California, USA

Material and method

Fifty-two male domestic pigs with a mean weight of 17.8 kg (SE ± 0.5) were premedicated with intraperitoneal azaperon (3 mg/kg) and metomidate (10 mg/kg) and anesthetized with sodium-pentobarbital. An initial intravenous bolus injection of 10–15 mg (pentobarbital) per kilogram bodyweight was followed by repetitive small intravenous doses to maintain anesthesia up to a maximum of 30 mg/kg. The animals were ventilated via an endotracheal tube with room air enriched with 2.0 l/min oxygen, using a pressure controlled BIRD Mark VII respirator. The thorax was opened at the fifth intercostal space, the pericardium was incised and the left circumflex coronary artery (LCCA) was dissected free. An ameroid constrictor (8 mm outer diameter, 5 mm length and 1.8–2.1 mm inner diameter) was placed around the left circumflex coronary artery (LCCA) distal to the first marginal branch in such a way that it did not produce a visible stenosis. The pericardium was left open, the chest was closed in layers and the pigs were allowed to recover. A broad spectrum antibiotic (tardomycel, 1 million I.U., Bayer) was injected on the day of surgery and 3 days after. Three thoracotomized animals with prepared coronary arteries, but without constrictors served as sham-operated controls. They were also allowed to recover and were studied 4 weeks after thoracotomy.

Experimental protocol

Four, 8, 12, and 26 weeks after the initial surgery the animals were premedicated and anesthetized as described above. The chest was opened and heparin was injected into the pulmonary artery. The hearts were electrically fibrillated, quickly excised and were connected to a Langendorff perfusion system that was filled with fresh, heparinized, filtered pig blood as previously described (13, 14). Hematocrit was kept at 25–28 %, resembling in vivo conditions in swine. The pH was maintained between 7.35 and 7.45 during the experiment with sodium bicarbonate as necessary, and temperature was held constant at 37.0 °C with a heat exchanger. The perfusion system consisted of a pressure-controlled roller pump (Stoeckert, Munich), a venous roller pump, two blood filters with a pore size of 25 μm (Bentley, Puerto Rico), and a blood oxygenator (BIO-5, Bentley, Puerto Rico). Total coronary flow was measured with an electromagnetic flow transducer (Gould Statham). Perfusion and peripheral coronary pressure (in the distal stump of the occluded left circumflex) were measured with strain gage transducers (P 23 Db Statham) and recorded together with other parameters on a linear recorder (Watanabe Mark VII WR 3101).

A vent was inserted into the left ventricle, two ECG electrodes were attached to the surface of the heart. Thereafter the hearts were defibrillated after which they started to beat empty. After a stabilization period of approximately 10 min, maximal vasodilatation was achieved by infusion of 1–2 ml of a 10 mM solution of adenosine into the aortic cannula until no further increase of flow could be achieved.

At 40, 60, 80, and 100 mm Hg perfusion pressure, differently labeled radioactive microspheres were injected to measure regional distribution of blood flow. The microspheres had a diameter of 8–10 μm. Prior to injection, the microsphere suspension was vigorously stirred and thereafter placed in an ultrasonic bath. This was mixed with 0.9 % NaCl-solution and injected into the perfusion line through a multiple hole catheter. Approximately 200000 beads of microspheres were injected per bolus.

At the end of the experiments the hearts were perfusion-fixed with formaldehyde or glutaraldehyde and the coronaries were filled with a radiopaque dye under a constant pressure of 95 mm Hg according to the protocol of Fulton (9). For post mortem angiography the hearts were irradiated with a point-like source of soft x-rays (28 keV, Machlett X-Ray Tubes, Inc., U.K., obtained from Balteau, S.A., Liege, Belgium) and radiograms were obtained from crystallographic x-ray film. Stereograms were obtained as described earlier (1). After the angiograms were taken, the ameroid constrictor was dissected free and the hearts were cut for microsphere counting as described before (10). Briefly, the hearts were cut into 0.7-cm-thick slices parallel to the heart base. Three of these slices were cut into about 30 to 40 consecutive sectors which were divided into epi-, mid- and endocardial layers and the specific radioactivity of the weighted samples was determined in a pulse-height analyzer (Nuclear Data 630, Frankfurt, FRG) coupled to an essential Germanium well-type detector as described previously (11). The remainder of the heart was dissolved in warm 5 N KOH and specific radioactivity was determined in 10 samples of the stirred suspension to calculate the total radioactivity of the heart. Using these data

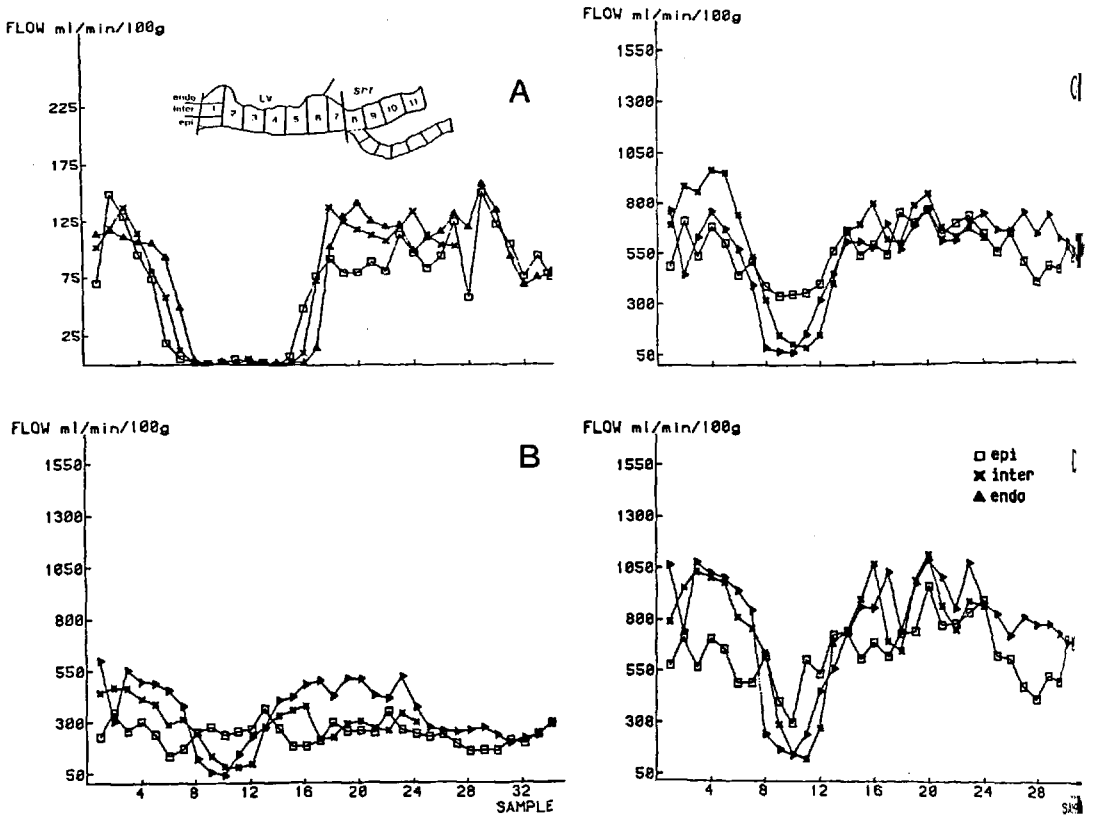

Fig. 1. The effect of acute (panel A) and of chronic (panels B, C, and D) coronary occlusion on blood flow in myocardium subtended by the left circumflex coronary artery. The insert in panel A demonstrates the "unrolling" of the left ventricle and of the interventricular septum (SPT), the sectioning into segments and into subepicardial, intermediate, and subendocardial samples. The sample address is on the abscissa, the flow is on the ordinate. Panels B, C, and D are from the same heart and the blood flow response to maximal vasodilation (adenosine-infusion) at 60 mm Hg (B), 80 mm Hg (C), and 100 mm Hg (D) perfusion pressure is depicted. Collateral flow (trough-like depression) in the subendocardium (triangles) and in the intermediate layers (crosses) is much lower than normal coronary flow. Subepicardial collateral flow does not rise as much as subepicardial flow to normal regions. The edges of the "trough" corresponded well with the visual delineation of the left circumflex coronary artery perfusion territory.

combined with the bulk flow, the regional flow in ml/min/100 g wet weight was calculated using the equation:

$$\text{sample flow} = \frac{\text{sample activity} \times \text{total flow}}{\text{total activity}}$$

Identification of collateral-supplied and normally perfused myocardium was made using the "flow map" at a perfusion pressure of 100 mm Hg using an interactive self-designed computer program (12) (see Fig. 1).

Table 1. Collateral blood flow is listed as a function of perfusion pressure and as a function of time after onset of coronary stenosis. Collateral blood flow at 4 weeks after ameroid implantation is significantly lower than that at 8, 12 and 26 weeks ($p < 0.05$). Normal flow in the table refers to percent of maximal normal-region flow at maximal coronary vasodilation.

	40 mm Hg	60 mm Hg	80 mm Hg	100 mm Hg	
4 weeks	18 %	14 %	14 %	14 %	% of normal flow
n = 5	8 %	5 %	5 %	5 %	± SD
8 weeks	49 %	44 %	47 %	46 %	% of normal flow
n = 6	17 %	35 %	27 %	24 %	± SD
12 weeks	54 %	51 %	61 %	66 %	% of normal flow
n = 6	34 %	25 %	26 %	25 %	± SD
26 weeks	54 %	49 %	49 %	51 %	% of normal flow
n = 4	24 %	26 %	24 %	23 %	± SD

Statistics

Values were compared by single and multifactorial analysis of variance, unpaired and paired *t*-test, and Kruskal-Wallis-Test.

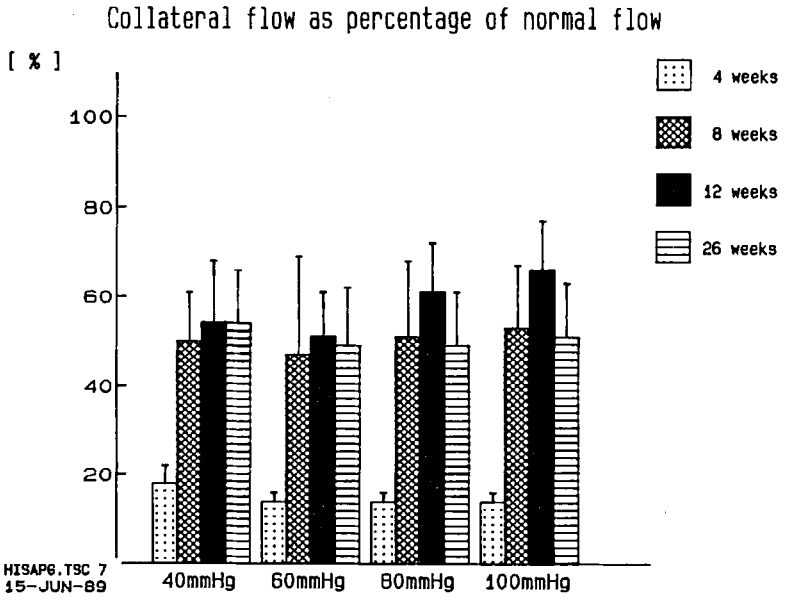

Fig. 2. Collateral blood flow is expressed as fraction of the normal region flow at maximal coronary vasodilation. Increases in blood flow are linearly related to perfusion pressure in maximally vasodilated beds, flow ratios remain invariant with perfusion pressure. Collateral flow at 4 weeks is significantly ($p < 0.01$) higher than that of sham-operated controls but significantly lower ($p < 0.05$) than that of 8, 12, and 26 weeks. Collateral flow remains invariant between 8 and 26 weeks after constrictor implantation.

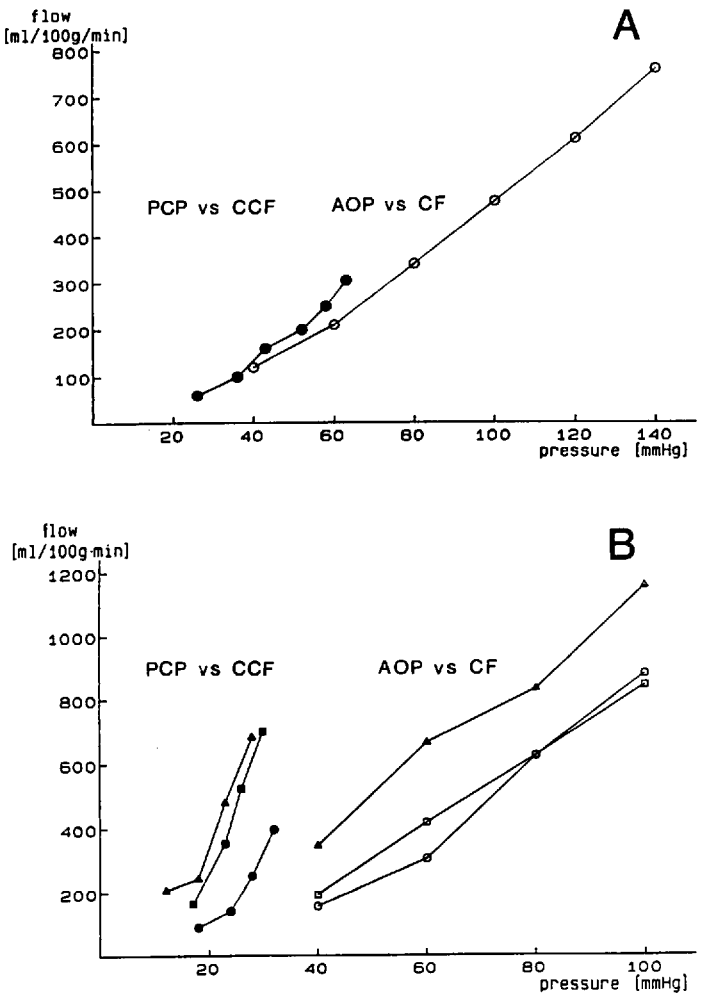

Fig. 3. Relationship between aortic perfusion pressure (AOP) and blood flow to the normal myocardium of hearts with one constricted coronary artery and between peripheral coronary pressure (PCP) and collateral blood flow (CCF).
Panel A: pressure flow relationships in dog hearts with chronic coronary occlusion (data from a previous report (14), replotted and in this form not previously published). The relationship PCP vs collateral flow overlaps with AoP vs coronary flow and suggests that minimal vascular resistance in the recipient bed was not changed.
Panel B: in the three pig hearts available for detailed pressure-flow studies the relationship PCP vs collateral flow is much steeper than that of AoP vs coronary flow, suggesting a substantially decreased minimal resistance of the recipient bed.

Results

A Exclusion criteria

Data were excluded when one of the following situations occurred:
1) death of the animal before the appointed experimental duration;

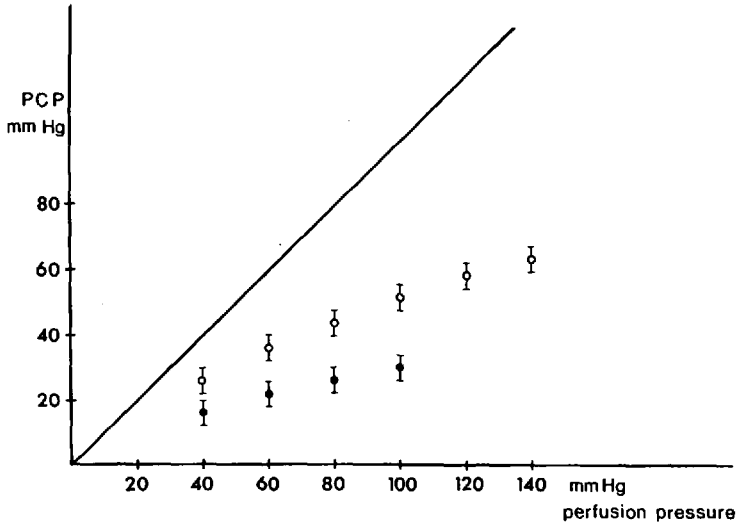

Fig. 4. Relationship between aortic perfusion pressure and peripheral coronary pressure (measured in the distal stump of the occluded artery) measured during maximal coronary vasodilation with adenosine. In canine hearts (open circles) PCP is much higher than in porcine hearts.

2) macroscopic myocardial infarction;
3) stenosed but not completely occluded left circumflex artery.

From the 49 pigs that underwent constrictor implantation, nine died suddenly between 14 and 28 days after surgery, apparently from ventricular fibrillation. Ten hearts were excluded because of large visible infarcts. In four hearts the constrictor was not completely occluded at four weeks and three hearts were rejected because of aortic insufficiency under the conditions of retrograde aortic perfusion. The data of two animals were rejected because of faulty microsphere calibration.

B Myocardial flow in control animals

Opening and closing of the chest and preparation of the coronary artery had no influence by itself on blood flow. Regional blood flow was homogeneously distributed in the three sham-operated controls. Epi-endo ratios were not changed in the LCCA bed.

C Electromagnetic and tracer microsphere flow in chronic coronary occlusion

Collateral blood flow and the relative proportion of collateral flow to normal region flow are depicted in Table 1 and Figs. 1 and 2. Blood flow increases linearly in response to increases in perfusion pressure in the presence of adenosine. In absolute terms these values are similar to those reported earlier for the dog (13, 14). There was no significant difference between groups with respect to total coronary flow. However, collateral flow was significantly lower 4 weeks after constrictor implantation compared to 8, 12, and 24 weeks. At 8, 12, and 24 weeks collateral flow was only about 50 % of maximal normal region flow. The relationship between peripheral coronary pressure and collateral blood flow and of aortic perfusion pressure vs normal region flow for the pig heart are depicted in Fig. 3B. They may be contrasted to the relationship obtained from the dog heart (Fig. 3A). The relationship of PCP vs collateral flow in the pig is much steeper than that of AoP vs coronary flow, a

behavior which significantly differs from that in the dog where the slopes of both curves are identical (13, 14).

D Tomo-angiograms

The angiogram of a heart slice is shown in Fig. 4. The denser vascularity in the region of the occluded artery is clearly visible. These vessels are of precapillary size but are vein-like in appearance. Close visual inspection of the angiogram verified that the contrast material was contained within many small vessels without extravasation of contrast material. Increased vascularity of the risk region was seen in all animals at all intervals studied.

Discussion

Our experimental data show that progressive coronary narrowing leading to chronic coronary occlusion in the pig causes the development of a collateral circulation that is potentially able to prevent myocardial infarction. We showed previously (15) that acute coronary occlusion in the pig leads to a complete loss of the entire region at risk of infarction. Slowly progressing coronary occlusion, as in the present study, leads to a complete preservation of the risk region. Visible infarctions did occur in 10 hearts out of 39 surviving animals but the potency of preservation by collateral growth is evident. The capability of pig collaterals to conduct blood to the risk region (50–60 % of maximal normal flow) is comparable to that observed in the dog heart (13, 14). There are, however, important differences between dogs and pigs in the way this result was achieved:

1) In the dog only a few large-bore epicardial collaterals develop, whereas in the pig numerous small vessels of the entire risk region (with a slight preference toward the subendocardium) participate in the growth adaptation.
2) Although similar values of collateral perfusion are obtained, the peripheral coronary pressure is significantly lower in the pig.

This can only mean that the minimal resistance of the risk region vasculature had decreased. The plot of peripheral coronary pressure vs collateral blood flow supports this hypothesis: in the dog this relationship is almost identical with the relationship between aortic pressure vs normal coronary blood flow (14). The peripheral coronary pressure is the true perfusion pressure of the recipient part of the coronary tree (13, 14). In the dog heart the native distal coronary system of the now occluded coronary artery is used as the distributing system of the coronary blood flow. Since it does not change its (anatomical) resistive characteristics, its pressure-flow relationship does not deviate from that of the normal coronary tree.

The angiographic patterns of the pig heart show marked differences with that of the dog: the filling of microvessels within the entire risk region is so pronounced that the impression of a "blush" prevails. These angiographic findings provide a likely explanation for the significantly lower peripheral coronary pressures observed in these pig hearts. Collateral flow in the pig heart must traverse these vascular connections which, although numerous, are of small caliber and provide a high flow resistance. Consequently, the drop in pressure across this collateral bed would be expected to be more pronounced than in the dog heart.

Under these conditions of a lower peripheral coronary pressure, maximal collateral coronary flow would be expected to be lower than measured in the dog unless other factors are operating. Since maximal collateral flow in the pig was, in fact, similar to the dog heart, we infer that the recipient peripheral coronary vascular bed of the pig heart has decreased its minimal resistance. The relationship (see Fig. 3B) between peripheral coronary pressure

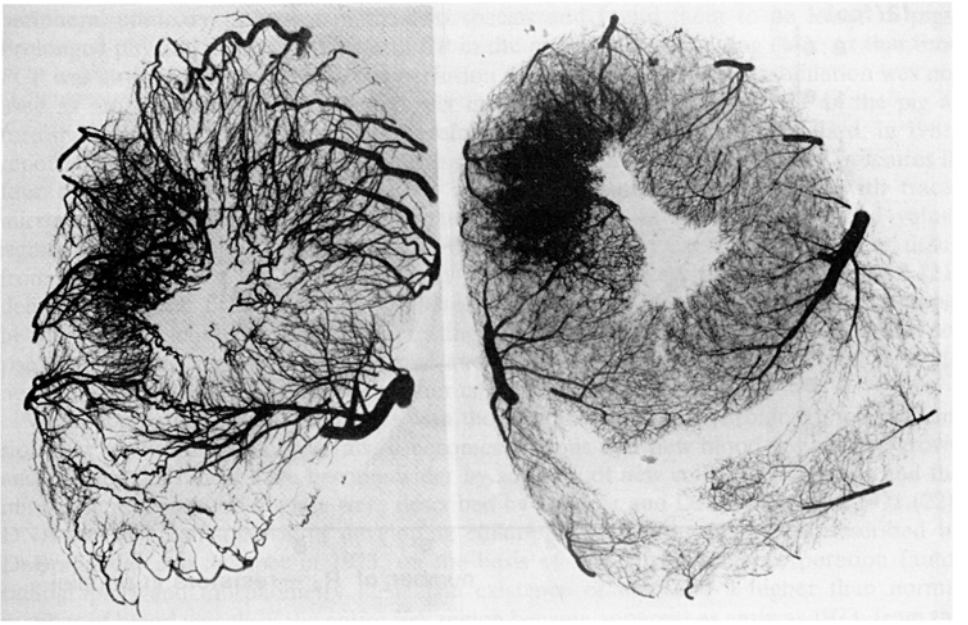

Fig. 5. Angiograms of heart slices after chronic coronary occlusion. Left panel: human heart with left circumflex coronary occlusion [used by permission from (9)]. Note the denser vascularity of the injected microvessels in addition to the well-developed subendocardial network of collaterals. Right panel: swine-heart slice with a chronically occluded left circumflex coronary artery and a dense "blush" of injected microvessels in the entire perfusion territory of the left circumflex bed.

and collateral flow is much steeper in the pig heart and is proof of the reduction of the minimal resistance of the recipient bed.

The interpretation of pressure-flow relationships as shown in Fig. 3 is, however, only valid if the LAD-resistance (R_{LAD} in Fig. 6) is not negligible and higher in the pig as compared to the dog. From these and previous experiments (3, 13, 14, 18) we found no evidence for a larger R_{LAD} in the pig.

Decrease of the minimal resistance of the recipient bed together with the decrease of collateral resistance appears to be a useful alternative when the initial collateral resistance is very high, as in the pig. There is little need for such an adaptation in the canine heart where a preexisting collateral system is able to increase in size when the need arises. The adaptation of the recipient bed microvasculature in the pig heart can be viewed as a parallel resistor in a network (see Fig. 6, insert). The usefulness (solely in terms of flow distribution) of this adaptation is limited as the model-simulation shows.

Finally we want to point out the similarities between the pig heart's reaction to chronic coronary occlusion with that of the human heart. The tomo-angiogram of a human heart with chronic coronary artery disease (see Fig. 5) shows a striking similarity with that of the pig. It serves as an example that focal coronary lesion can lead to a complete remodeling of the entire coronary tree.

Limitations of the model

We have shown in this report that in spite of the paucity of collaterals in the pig heart, maximal collateral flow (per unit of volume of myocardium) can be as high as that obtained

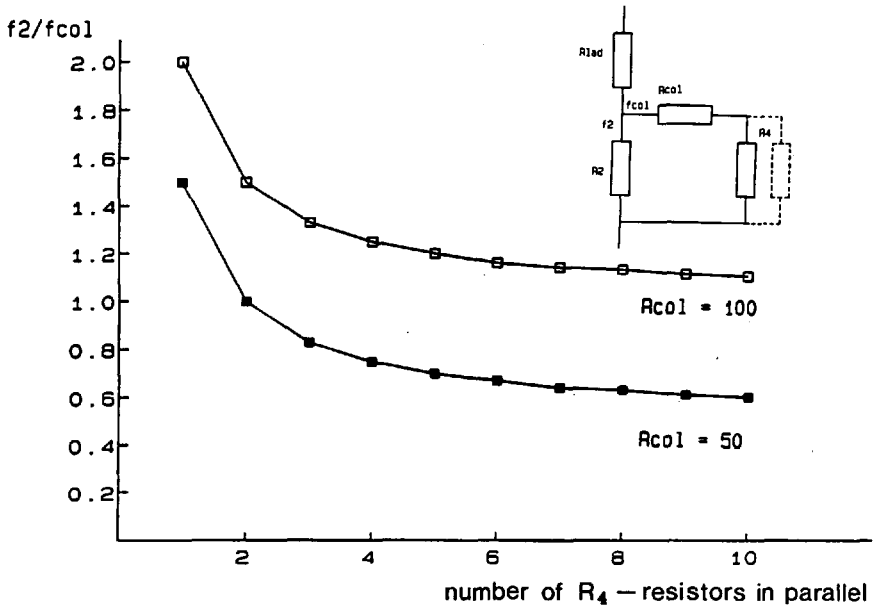

Fig. 6. Insert upper right: resistive network model of the coronary and collateral circulation. It is assumed that the circumflex risk region (R_4) is supplied via collaterals (R_{col}) from the left anterior descending artery (R_{LAD}). R_2 is the lumped microcirculatory resistance of the normal unstenosed region; at the beginning of the experiment it is identical to R_4. The growth of new vessels in the risk region is depicted as resistors parallel to R_4. The effect of resistors parallel to R_4 on the relationship of coronary flow to collateral flow (f_2/f_{col}) is studied in the model of the insert. The largest effect is obtained by adding one and two resistors in parallel to R_4, addition of more resistors has only little additional effect. Solid symbols: effect of parallel resistors after growth-induced decrease of R_{col}. The calculation is shown for two values of the collateral resistance (R_{col}).

in the dog. The similarity is, however, more apparent than in reality because this result was only obtainable with a relatively small risk region in the pig. Previous experience had shown that occlusions of the dominant right coronary artery, the left anterior descending artery and even of the proximal left circumflex artery (the smallest of the epicardial coronary arteries) are poorly tolerated in the pig: mortality by incidence and size of infarcts is so high that the usefulness of such experiments decreases sharply. There is therefore no doubt that canine hearts tolerate coronary occlusion (even multiple occlusions) better. It remains to be elucidated why maximal collateral flow in the canine is not higher than that in the pig.

Literature review

The paucity of anatomically demonstrable collaterals in the pig was already known to Blumgart et al. in 1950 (15): only in one of 44 pigs anastomoses could be demonstrated. Similar findings were reported by Vastesaeger (16). Retrograde flow was measured by Eckstein (17) in 1954, and found to be much lower than in dogs. Lumb (6), in 1964, constricted coronary arteries in the pig and demonstrated by post mortem angiography the development of collaterals. Schaper et al. (3), in 1967, described the predilection sites of developed collaterals in the pig (the papillary muscles) and measured the peripheral coronary pressures in pigs and dogs. In a later study (18) these authors compared the

peripheral coronary pressures in the two species and found them to be lower in pigs. Prolonged physical exercise increased PCP in the pig but not in the dog (18). At that time PCP was already referenced to aortic perfusion pressure, but maximal vasodilation was not used as an experimental tool. The correct interpretation of the lower PCP in the pig as furnished with this report remained, therefore, uncertain for some time. Millard, in 1981, reported PCPs obtained from six pigs with developed collaterals with very low pressures in four of the six (19). Bloor et al. (20), in 1984, measured collateral flow with tracer microspheres following chronic left circumflex occlusion in the pig and found values significantly lower than in normal-region-flow, although they excluded visible scar tissue from the analysis. In a more recent study Roth and coworkers from Bloor's group (21) demonstrated that collateral flow in ameroid-occluded left circumflex regions of minipig hearts was sufficient to support normal resting contractile function but collateral flow did not rise during moderate and severe exercise and contractile function fell. Collateral flow did not improve between 7 and 16 weeks after constrictor implantation.

When comparing normal pig hearts with those after progressive chronic coronary occlusion that had developed collaterals, it becomes obvious that new blood vessels had grown and existing ones must have become wider by addition of new cells. Angiogenesis and the mitogenic response to ischemia were described by Schaper and DeBrabander in 1971 (22). DNA-synthesis and mitosis in developing collaterals of the pig heart was described by DeBrabander and Schaper in 1973, on the basis of 3-H-Thymidine incorporation (autoradiography) and morphometry (23). The existence of new and a higher than normal number of blood vessels in the entire risk region became apparent as early as 1973, from the quantitative histology, but the improved microangiography with soft x-rays as in the present study and the steeper relationship between PCP and collateral flow made this generalized angiogenic response visible.

The non-sprouting angiogenic response to ischemia that we described in the past (22, 23) was originally believed to be caused by the abnormal distribution of physical forces like tangential wall stress (24) or viscous drag (25). We postulated (2) and favored the existence of biochemical transmitters because mitosis and DNA-synthesis occur (although at a lower rate) also in small veins accompanying growing collaterals where the distribution of physical forces differs, and we recently (26) isolated potent mitogenic peptides of the Fibroblast Growth Factor family (27, 28, 29) from bovine, porcine, and canine hearts. The role of these peptides in the process of vascular growth remains to be elucidated.

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