The Stimulation of Cardiac Prostaglandin Production by Blood Plasma and Its Relationship to the Regulation of Coronary Flow in Isolated Isovolumic Rabbit Hearts

RICHARD L. MORETTI, PH.D., S. ABRAHAM, PH.D., AND ROGER R. ECKER, M.D.

SUMMARY Infusion of small amounts of blood plasma into isolated, isovolumic rabbit hearts perfused with Tyrode's solution resulted in coronary vasoconstriction followed by a decrease in left ventricular developed pressure and dP/dt. Maximal effects were obtained with a perfusate plasma concentration of 1%. Increasing the plasma concentration beyond 1% did not appreciably increase the coronary vasoconstriction. During perfusion with 2% plasma, the coronary flow-oxygen uptake ratio was unchanged over a range of perfusion pressures (40-100 mm Hg) and vascular resistance increased with pressure. In the absence of plasma, the coronary flow-oxygen uptake ratio increased with pressure and vascular resistance decreased. Thus, cardiac regulation of coronary flow is response to changes in perfusion pressure occurred in the presence of plasma but not in its absence. The effects of plasma were reduced with two different inhibitors of prostaglandin synthesis (5,11,14-eicosatetraynoic acid and indomethacin). At a perfusate concentration of 50 μg/ml, indomethacin abolished the effects of 2% plasma. Rat stomach strip bioassay for prostaglandin activity indicated that the vasoconstrictor effect of plasma was accompanied by a 4-fold increase in the release of prostaglandin activity by the isolated hearts. The vasoconstrictor effect of plasma also was accompanied by an increase in the conversion of 1H-arachidonate to radiolabeled prostaglandins E₁ and F₂α. These results indicate that a relationship exists between a coronary vasoconstrictor in plasma, cardiac prostaglandin synthesis, and the regulation of coronary flow in response to changes in perfusion pressure in isolated rabbit hearts.

SEVERAL reports suggest that the presence of blood or plasma in the coronary perfusate is essential for maintenance of the normal relationship between coronary flow rate and myocardial activity. When isolated hearts were perfused with blood from support animals, coronary flow rates were within the physiological range.1,2 When perfused with physiological saline solutions, the flow rates were much higher.3-6 The difference in flows is greater than expected on the basis of viscosity differences, suggesting a greater coronary vasoconstriction during blood perfusion than occurs during perfusion with physiological saline solutions. The possibility that blood may cause constriction of coronary arteries is supported by evidence from experiments on isolated coronary arterial strips. When the saline solution bathing the strips was replaced with blood or plasma, marked contractions occurred.

When dog hearts were perfused with blood in situ and myocardial activity was constant, coronary resistance increased as perfusion pressure was increased.8 In contrast, isolated rabbit hearts perfused with mammalian Ringer's solution showed as a function of perfusion pressure a decrease in coronary resistance accompanied by a marked increase in flow.9 Since myocardial activity was neither measured nor controlled in the experiments on rabbits, the results are difficult to interpret. They do suggest, however, that regulation in response to changes in perfusion pressure occurs during blood perfusion, but not during perfusion with a physiologic salt solution.

To explore this question further, we studied the action of blood plasma on the coronary vasculature and examined its role in the regulation of coronary flow in response to changes in perfusion pressure in isolated isovolumic rabbit hearts. The results of these experiments led to an investigation of the relationship between the action of plasma and cardiac prostaglandin production.

Methods

ISOVOLUMIC ISOLATED HEART PREPARATION

Hearts were excised from New Zealand white male rabbits (2-3.5 kg) which received intravenous injections of sodium pentobarbital (45 mg/kg) for anesthesia and heparin (200 U/kg). Each excised heart was placed in cold (0°C) Tyrode's solution, the aorta was cannulated, and the heart then was attached by the cannula to a perfusion manifold. Care was taken to exclude air from the heart and cannula. Pressure and temperature of the perfusate were monitored through fittings in the perfusion manifold. We used an automatic infusion pump to infuse test solutions into the perfusate through additional fittings in the manifold.

A drain with an inside diameter (i.d.) of 1.5 mm was inserted through the pulmonary artery into the right ventricle and secured with a suture around the artery. The venae cavae were ligated. Coronary flow was measured by timed collections from the drain. Left ventricular pressure was measured with a fluid-filled isovolumic balloon catheter which was inserted into the left ventricle through a slit in the...
tein precipitate again was filtered and washed, then dried dissolved in 95% ethanol (12 mg/ml). Atropine (Sigma) was remove ether traces. The LDP preparations were stored at 5°C, then dissolved in Tyrode's solution before use.

**CHEMICALS**

The lipids used were: tritium-labeled arachidonic acid (5,6,8,9,11,12,14,15-3H), 72 Ci/mmol (New England Nuclear); unlabeled arachidonic acid (Sigma); prostaglandins (Upjohn) (prostaglandins E\(_1\), E\(_2\), F\(_2\), as acids, prostaglandin F\(_{2\alpha}\) as the tromethamine salt); and 5,8,11,14-eicosatetraynoic acid (TYA) (Hoffman-LaRoche). These fatty acids were dissolved in a small volume of ethyl acetate and applied to silica gel thin layer chromatography plates (Quantum Industries). The plates were developed with benzene-dioxane-acetic acid, 20:20:1, sprayed with anisaldehyde, and heated at 90°C for 5 minutes. The regions containing prostaglandins E and F, and adjacent control regions, were eluted and their radioactivity was determined by liquid scintillation counting.

**BLOOD PREPARATIONS**

Venous and arterial rabbit plasma was prepared at room temperature by centrifugation of blood drawn from the inferior vena cava or the left ventricle of heart donors just prior to excision of the heart. Plasma either was used immediately or was stored by freezing at -20°C. Venous and arterial preparations produced similar results in all experiments. Lipid-deficient plasma protein (LDP) was prepared by a method which removed over 98% of the lipids. Plasma (10 ml, 5°C) was mixed for 2 hours at -20°C with 240 ml of precooled (-20°C) ethanol-diethyl ether (3:1). The precipitated proteins were collected by filtration, washed and their radioactivity was determined by liquid scintillation counting.

**EXTRACTION AND MEASUREMENT OF RADIOLABELED PROSTAGLANDINS**

Prostaglandins were extracted from acidified (pH 2.5) samples of coronary effluent (20-30 ml) with ethyl acetate. Unlabeled prostaglandins E\(_2\) and F\(_{2\alpha}\) (10 µg each) were added to the samples as carriers. The ethyl acetate extracts were evaporated in vacuo at 20°C; the residues were dissolved in a small volume of ethyl acetate and applied to silica gel thin layer chromatography plates (Quantum Industries). The plates were developed with benzene-dioxane-acetic acid, 20:20:1, sprayed with anisaldehyde, and heated at 90°C for 5 minutes. The regions containing prostaglandins E and F, and adjacent control regions, were eluted and their radioactivity was determined by liquid scintillation counting.

**RESULTS**

**EFFECT OF PLASMA ON CORONARY FLOW AND MYOCARDIAL ACTIVITY**

Hearts were perfused with Tyrode's solution until coronary flow, left ventricular developed pressure, and heart rate reached steady values. Plasma then was added to Tyrode's solution and infused at a constant rate. Within 1 minute coronary flow declined and this was followed by decreases in developed pressure and dP/dt (Fig. 1). In about 2 minutes, low levels were reached which persisted until the plasma infusion was stopped. Flow and pressure values returned to their original levels in 5-6 minutes. Repeated observations could therefore be made on the same heart, and each heart could act as its own control.

The effect of plasma was dose-dependent up to a perfusate concentration of about 1%. Only slightly greater effects were observed at higher concentrations (Fig. 2). Coronary flow was decreased by 65% with 1% plasma. The viscosity of 1% plasma, calculated from the data of Merrill or from our measurements using a capillary viscometer, accounts for less than 1% of the decrease in flow. Thus, the decreases in coronary flow must have been due to an increase in vascular resistance.

Coronary flow decreased before contractions weakened (Fig. 1), suggesting a primary effect on the coronary vasculature. Since maximal effects were obtained with such low levels of plasma, the substance responsible for vasocostriction must be present in excess in circulating blood. Moderate or even large fluctuations in its blood concentration should have little effect on coronary flow.
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EFFECT OF PLASMA ON REGULATION OF CORONARY FLOW

In these experiments, hearts were perfused alternately with either Tyrode's solution or 2% plasma in Tyrode's solution. The perfusion pressure was increased, in increments of 20 mm Hg, from 40 mm Hg to 100 mm Hg. When hearts were perfused with 2% plasma, increases in perfusion pressure caused moderate increases in coronary flow and oxygen uptake (Fig. 3A and B), but the coronary flow-oxygen uptake ratio remained unchanged (Fig. 3C) and vascular resistance increased (Fig. 3D). In contrast, when perfused with only Tyrode's solution, increases in perfusion pressure caused disproportionate increases in coronary flow (Fig. 3A). The coronary flow-oxygen uptake ratios increased (Fig. 3C) while vascular resistance declined (Fig. 3D). Hence, the hearts regulated their coronary flow in response to increases in perfusion pressure in the presence of plasma but not in its absence.

The increase in vascular resistance observed in the presence of plasma must have been due to coronary vasoconstriction in response to pressure. Plasma could supply a substance which is essential for this response but which is not contained within the heart. Since blood causes contraction in isolated rat stomach strips as well as arterial strips, and since prostaglandins cause contraction in rat stomach strips and are vasoactive, we explored the possibility of a relationship between plasma and prostaglandins in isolated rabbit hearts. Initially, the effects of inhibitors of prostaglandin synthesis on the action of plasma were examined. To decrease the possibility of nonspecific effects, two structurally different inhibitors were employed, indomethacin and 5,8,11,14-eicosatetraynoic acid (TYA).

EFFECT OF INHIBITORS OF PROSTAGLANDIN SYNTHESIS

Hearts were perfused alternately with either Tyrode's solution or 2% plasma in Tyrode's solution. The perfusion pressure was maintained at 60 mm Hg while indomethacin or TYA was infused into the perfusate. Equimolar concentrations of these inhibitors produced similar results; those obtained with indomethacin are summarized in Figure 4. Either in the presence or absence of plasma, these inhibitors caused an increase in flow rate and the flow rate-oxygen uptake ratios. The dose-response curves for the ratios paralleled those for coronary flow. Hence, the increase in coronary flow was in excess of that required to maintain the oxygen supply. Much higher concentrations of both inhibitors were required to produce an effect in the presence of plasma. However, high inhibitor concentrations abolished the vasoconstrictor effect of plasma; when the perfusate concentration of indomethacin was 50 μg/ml, the infusion of plasma did not result in a decrease in coronary flow.
These results suggest a relationship between the action of plasma and cardiac prostaglandin synthesis. They also suggest a possible mechanism. More indomethacin is required to inhibit prostaglandin synthesis in the presence of high substrate levels than when low levels are employed. Since more indomethacin or TYA was required to produce coronary vasodilation in the presence of plasma, perhaps plasma acts by providing a precursor or cofactor for cardiac prostaglandin synthesis.

This possibility first was examined in studies on rat stomach strips, in which both blood and arachidonate cause contractions. The strips were prepared as described herein for the prostaglandin bioassay except that indomethacin initially was omitted from the superfusate. Indomethacin was added as indicated in Table 1. Plasma and arachidonate both caused the strips to contract. Indomethacin inhibited the effects of both plasma and arachidonate. When the concentration of arachidonate was increased, more indomethacin was required to abolish the contraction (Table 1). When precursors of prostaglandin synthesis, such as arachidonate, were removed from plasma by extraction of the plasma lipids, the lipid-deficient plasma protein (LDP) retained only about 5% of the original activity (Table 2).

These results are in accord with the supposition that plasma might act by providing a precursor for prostaglandin synthesis. However, when arachidonate and preparations of LDP were tested in isolated rabbit hearts, unexpected results were obtained. The coronary vasoconstrictor activity of LDP preparations was compared to that of plasma by using the initial slope of the dose-response curve (Fig. 2) as the basis for an assay. Each LDP preparation was dissolved in Tyrode’s solution to give a protein concentration equal to that of the original plasma. When infused into isolated hearts, the LDP preparations were found to retain most of the vasoconstrictor activity (Table 3). One LDP preparation had only 42% of the original activity but all others retained more than 80%. When arachidonate (1-5 μg/ml of perfusate) was infused into isolated rabbit hearts for periods of up to 10 minutes, it had no effect on coronary flow, either in the presence or absence of the coronary vasoconstrictor in plasma.

These results show that the vasoconstrictor is neither arachidonate nor the blood component which causes contraction of the rat stomach strips. However, the vasoconstrictor effect of LDP could be inhibited with indomethacin; the greater the vasoconstrictor activity of the LDP preparation, the more indomethacin required for inhibition (Fig. 5A). Thus, the results are consistent with the suggestion that a relationship between the coronary vasoconstrictor and cardiac prostaglandin synthesis does exist. This possi-
A. Coronary Flow (CF)

**TABLE 1**

<table>
<thead>
<tr>
<th>Indomethacin concentration (µg/ml)</th>
<th>0</th>
<th>3</th>
<th>10</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonate, 2 µg/ml</td>
<td>39</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arachidonate, 16 µg/ml</td>
<td>60*</td>
<td>60*</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Plasma, 0.5%</td>
<td>55 ± 1</td>
<td>33 ± 5</td>
<td>21 ± 3</td>
<td>15 ± 3</td>
</tr>
</tbody>
</table>

Values are expressed in millimeters of pen deflection. Values for plasma (mean ± s.e.) were obtained from plasma from three rabbits. Addition of indomethacin to the superfusate caused the strips to relax; tests were conducted after relaxation was complete. See Methods for additional experimental details.

* Greater than full scale deflection.

Cardiac synthesis of prostaglandins was evaluated further by infusing 1H-arachidonate into hearts and analyzing the coronary effluent for 1H-labeled prostaglandins with the aid of thin layer chromatography. Radioactivity was recovered from the regions of the chromatograms containing prostaglandins E and F (Table 4). Perfusion with LDP increased the amount of label recovered from both these regions. Since prostaglandins E₅ and F₆ are formed from arachidonate, these data show that the coronary vasoconstrictor stimulated the synthesis of both these prostaglandins.

The effects of exogenous prostaglandins on coronary flow in isolated hearts also was examined. The prostaglandins first were bound to albumin to reduce the possibility of nonspecific depressant effects. The prostaglandins were infused at rates which produced concentrations from 0.1 ng/ml to 5.0 µg/ml. Prostaglandins E₅ and E₆ had no effect in concentrations up to 50 ng/ml. In high concentrations (0.5-5.0 µg/ml) prostaglandins E₅ and E₆ caused an increase in coronary flow, whereas prostaglandins F₅ and F₆ caused a decrease in flow. These effects were

**TABLE 2**

<table>
<thead>
<tr>
<th>Plasma no.</th>
<th>Plasma (ng PGE₁-eq/ml)</th>
<th>LDP</th>
<th>Vasoreactivity of LDP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>325</td>
<td>16</td>
<td>104</td>
</tr>
<tr>
<td>2</td>
<td>372</td>
<td>20</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>390</td>
<td>27</td>
<td>42</td>
</tr>
</tbody>
</table>

Stomach strip contractions caused by test samples were compared with those caused by standard amounts of prostaglandin E₅ (PGE₁). The vasoreactivity activity for each LDP preparation is expressed as a percent of the activity of the plasma from which it was obtained. See text for additional experimental details.
TABLE 3  Effect of Lipid-Deficient Plasma Protein (LDP) on Coronary Flow and Release of Prostaglandin-like Activity in Isolated Rabbit Hearts

<table>
<thead>
<tr>
<th>Heart no.</th>
<th>LDP preparation no.</th>
<th>Prostaglandin-like activity (ng PGE$_2$ eq/min per g of heart)</th>
<th>Coronary flow (ml/min per g of heart)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tyrode's</td>
<td>LDP</td>
</tr>
<tr>
<td>120</td>
<td>1</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>121</td>
<td>2</td>
<td>0.08</td>
<td>0.36</td>
</tr>
<tr>
<td>122</td>
<td>2</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>123</td>
<td>4</td>
<td>0.02</td>
<td>0.23</td>
</tr>
<tr>
<td>124</td>
<td>3</td>
<td>0.07</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td></td>
<td>0.06 ± 0.01</td>
<td>0.26 ± 0.04</td>
</tr>
</tbody>
</table>

Contractions of rat stomach strips produced by test samples were compared with those caused by standard amounts of prostaglandin E$_2$ (PGE$_2$). See text for additional experimental details.

Discussion

When a vascular system is unregulated its resistance to flow decreases with increasing transmural pressure due to passive distention of the vessels. When the isolated rabbit hearts were perfused with Tyrode's solution, an increase in perfusion pressure caused a decrease in vascular resistance. This change could not have been due to an increase in myocardial oxygen uptake because the coronary flow-oxygen uptake ratio increased markedly in the absence of plasma. During perfusion with 2% plasma, the vascular resistance increased as a function of pressure and thus attenuated the increase in flow. The increase in flow, in the presence of plasma, was just enough to meet the additional oxygen requirements (Fig. 3A and C). Therefore, cardiac regulation of coronary flow in response to changes in pressure was good in the presence of plasma, but inadequate in its absence. This indicates that there must be a component of plasma, a coronary vasoconstrictor, that is essential for the regulation of coronary flow by isolated rabbit hearts in response to changes in perfusion pressure.

Our results suggest a relationship between the action of the coronary vasoconstrictor and prostaglandin synthesis. The vasoconstrictor stimulates the synthesis by the isolated hearts of prostaglandins E$_2$ and F$_2\alpha$ from $^3$H-arachidonate. This synthesis is accompanied by the release of biological activity that is inhibited by either indomethacin or TYA. Furthermore, a concentration-dependent antagonism between the coronary vasoconstrictor and both prostaglandin synthetase inhibitors was seen. Block et al. found that anoxia blocked the release of prostaglandin-like activity and produced an increase in coronary flow in isolated rabbit hearts. These investigators failed to find an effect of indomethacin (1-2 µg/ml) on the basal coronary flow rate. However, we found that the increase in flow produced by an increase in myocardial oxygen uptake because the coronary flow-oxygen uptake ratio increased markedly in the absence of plasma.

![Figure 5](http://example.com/figure5.png)

**Figure 5** Effects of indomethacin on coronary flow (A) and on the release of prostaglandin activity (B) by isolated, isovolumic, perfused rabbit hearts. Perfusion pressure, 60 mm Hg, temperature, 37°C; perfusates, Tyrode's solution or lipid-deficient plasma protein (LDP) in Tyrode's solution (0.6 mg/ml). Data are from three LDP preparations tested in four hearts. Numbers in parentheses indicate the percent vasoconstrictor activity of each preparation (Table 3).
indomethacin concentration of 2 μg/ml occurs so slowly that it is difficult to discern, even in the absence of plasma.

Since our results and those of others indicate that hearts synthesize prostaglandins continuously, it is tempting to speculate that this synthesis aids in the maintenance of coronary vascular tone. Our data indicate that the degree of vasocostriction is directly proportional to the rate of prostaglandin synthesis. This is of interest because molecular (gaseous) oxygen is required in the synthesis of prostaglandins. If oxygen were rate-limiting, then a decrease in oxygen supply would result in a decrease in prostaglandin synthesis and an increase in coronary flow. In this regard, the venous PO₂ as reflected in the coronary flow-oxygen uptake ratios (Fig. 3C) was constant during perfusion with plasma or LDF, but in their absence, or when their effects were inhibited with either indomethacin or TYA, the venous PO₂ not only increased markedly but varied considerably.

Although our data are consistent with the supposition that cardiac prostaglandin synthesis plays a central role in the regulation of coronary blood flow, they do not eliminate other possibilities. The impressive evidence showing a relationship between coronary vasodilation and adenosine in the local regulation of coronary flow must be considered. Furthermore, there are some inconsistencies between our results and those of others. Needelman et al. reported that bradykinin caused a transient decrease in vascular resistance accompanied by an increase in release of prostaglandins of the E type in isolated rabbit hearts perfused with Krebs-Henseleit medium. Indomethacin (0.3 μg/ml) inhibited both the increase in flow and the release of prostaglandin activity. Kalsner found that indomethacin, aspirin, or TYA induced contractions of isolated bovine coronary arterial strips while concurrently decreasing the production of E-type prostaglandins. In studies on isolated, blood-perfused, canine heart-lung preparations, Alexander et al. found that indomethacin (3.5 μg/ml) reduced both reactive hyperemia and cardiac prostaglandin E₂ production, but had no effect on adenosine-induced coronary vasodilation. Hence, under various conditions, coronary vasodilation may be accompanied by a decrease, an increase, or no change in the release of prostaglandins of the E type. Our data show that plasma-induced coronary vasocostriction is accompanied by an increased synthesis of both prostaglandins E₂ and F₆, whereas prostaglandins E₃ and E₆ caused vasodilation.

Exogenous prostaglandins were without effect in amounts equivalent to 1 to 10 times the prostaglandin activity found in the coronary effluent. When administered in similar doses, prostaglandin E₂ was without effect on isolated rabbit hearts perfused with Krebs-Ringer solution. The inactivity of prostaglandins at these concentrations does not exclude involvement of cardiac prostaglandin synthesis in coronary vasocostriction or regulation of coronary flow. Both prostaglandins E₂ and F₆ are released by platelets during aggregation. Neither of these induces aggregation, but the endoperoxide prostaglandin G₂ does. This labile prostaglandin formerly was considered only as an intermediate in the synthesis of prostaglandins E₂ and F₆. Evidence also has been presented which suggests that the rabbit aorta-contracting substance is a prostaglandin intermediate. Hence, such an intermediate could be responsible for the coronary vasocostriction that we observed.

Our results could provide an explanation for some of the conflicting reports by others concerning the involvement of prostaglandins in the regulation of coronary flow. Experiments on isolated hearts perfused with solutions that did not contain blood or plasma usually produced high coronary flow rates. We have found prostaglandin synthesis to be minimal under these conditions and regulation of coronary flow, at least in response to changes in perfusion pressure, to be impaired. In experiments on blood-perfused hearts the amount of prostaglandin synthetase inhibitor used may have been insufficient. Our data indicate that inhibition by indomethacin or TYA is dependent on the relative concentrations of inhibitor and plasma. Indomethacin concentrations of about 20 μg/ml were required to produce a significant effect in the presence of 2% plasma. Assuming a linear relationship, concentrations of about 1 mg/ml would be needed to produce a direct effect in hearts perfused with whole blood. This is in excess of the amounts employed in experiments with blood-perfused hearts.

Acknowledgments

We thank Dr. John E. Pike, The Upjohn Company, for the gift of prostaglandin used in this study, and Hoffman-LaRoche, Inc., for the eicosatetraynoic acid.

References

Myocardial Necrosis, Fibrosis, and DNA Synthesis in Experimental Cardiac Hypertrophy Induced by Sudden Pressure Overload

SANFORD P. BISHOP, D.V.M., PH.D., AND LAWRENCE R. MELSEN

SUMMARY The development of myocardial fibrosis as a result of cardiac hypertrophy was studied in 11 cats in which the pulmonary artery was banded, and eight cats with congenital anomalies. Histological examination of the myocardium revealed multifocal areas of degeneration and necrosis with healing by fibrosis in the right ventricle of cats in which the pulmonary artery was banded and in the left ventricle of rabbits in which the aorta was banded. In five of eight cats with congenital anomalies, myocardial necrosis and fibrosis were not present in spite of heart weight to body weight ratios 2-4 times greater than in the experimental models. In the other three cats, fibrosis was subendocardial or diffuse rather than multifocal as in the banded animals. This suggests that the increased connective tissue found in animals with cardiac hypertrophy induced by banding the aorta or pulmonary artery is an artifact of the preparation. Autoradiographic studies of the myocardium of pulmonary artery-banded cats indicated that all newly synthesized DNA is in this model is restricted to interstitial cell and endothelial cell proliferation.

BANDING of the pulmonary artery or aorta is one of the most widely used methods for producing myocardial hypertrophy in experimental animals. Cardiac hypertrophy is produced readily by this method and the model has been used for study of a variety of functional,

1-11 biochemical,

12-14 and morphological

15-17 changes occurring during the development of hypertrophy. Sudden banding of a major vessel to a degree sufficient to produce cardiac enlargement, however, does not closely resemble the course of the events which occur during the gradual development of hypertrophy due to naturally occurring disease states in animals or man.

 Morphological alterations induced in an experimental model should be compared with those present in the naturally occurring condition in the same species and with those in man, to whom experimental results often are extrapolated.

The role of hyperplasia vs. hypertrophy of cardiac myocytes in the process of cardiac enlargement has been studied by several investigators. Determination of DNA content in experimental models of cardiac hypertrophy has generally shown that DNA concentration is the same as or increased compared to controls, indicating an increased total DNA content in the enlarged heart.

18-20 However, it has been shown by autoradiographic localization of tritiated thymidine uptake in the rat heart following banding of the aorta, that the newly synthesized DNA is restricted almost completely to nonmuscular cellular elements in the myocardium.

11-13, 15, 16, 17, 21 Therefore, in the rat model with aortic stenosis, there does not appear to be hyperplasia of myocardial muscle cells, but only of connective tissue and endothelial cells. The degree of connective tissue response in the myocardium of hypertrophied hearts is dependent on the
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