HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Negative metabolic and coronary flow effects of decreases in cAMP and increases in cGMP in control and renal hypertensive rabbit hearts

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Hypertension can lead to major alterations in myocardial signal transduction, especially in the nitric oxide and β-adrenergic signal transduction systems (1, 3). Manipulation of these signaling systems is often used to control blood pressure (3, 7, 19). This may have serious effects on cardiac function. There are alterations in the cardiac responses to the second messengers cAMP and cGMP in renal hypertensive rabbits (4, 16, 20, 27). It is not clear how the myocardial effects of these second messengers, which could lower pressure, will affect coronary blood flow, cardiac function, and metabolism.

The cyclic nucleotides cAMP and cGMP have been identified as important antagonistic metabolic and functional second messengers in myocardial cells (14). cGMP and nitric oxide have been shown to exert significant negative metabolic and functional effects on the heart (14, 17, 28). The actions of cGMP may be mediated through protein phosphorylation, interactions with other second messengers, i.e., cGMP-stimulated- or inhibited-cAMP phosphodiesterases, and direct and indirect inhibition of L-type calcium channels, leading to reductions in intracellular calcium (5, 13, 18, 24, 25). In the rabbit heart, previous work has demonstrated that changes in nitric oxide and/or cGMP levels lead to inverse changes in coronary flow and myocardial O2 consumption (6, 20, 309). These effects may offset the positive inotropic and metabolic effects of cAMP (6, 18, 25). cGMP has been shown to shorten action potential duration, decrease O2 consumption, and cause negative inotropy (14, 23, 24, 30). cAMP has been shown to cause positive inotropy and also increase myocardial metabolic function (2, 8, 12, 15, 21). Increased cAMP causes positive inotropy through increased calcium current, the inward influx of calcium responsible for the initiation of cardiac contraction (8, 15, 18). There is experimental evidence suggesting that cAMP not only increases the mean open time of each calcium channel but also increases the number of open channels (25). It has also been demonstrated that alterations in cGMP can affect the level of cAMP in the heart and myocytes (10, 12). This has suggested that an interaction exists between the second messenger systems mediated by cAMP and cGMP in the regulation of myocardial function.

In this study, we investigated the potential interaction between the second messengers cAMP and cGMP on coronary blood flow, metabolism, and function in control and hypertensive rabbit hearts. We tested the hypothesis that the negative myocardial effects of increasing the level of cGMP would be enhanced by lowering the level of cAMP and that this interaction would be altered by hypertension. This hypothesis was tested in control and renal hypertensive [1 kidney, 1 clip (1K1C)] New Zealand White rabbits. The level of cGMP was increased with an analog [8-bromo-cGMP (8-Br-cGMP)], and β-adrenergic blockade with propranolol (Prop) was used to lower the myocardial level of cAMP. We examined the effects...
of these agents alone and in combination on coronary blood flow, myocardial metabolism, and function in control and renal hypertensive rabbit hearts.

MATERIALS AND METHODS

Experimental preparation. New Zealand White rabbits (2–3 kg; n = 48) were used under a protocol approved by our Institutional Animal Care and Use Committee in accordance with the Guide for the Care of Laboratory Animals (Department of Health and Human Services publication no. 85-23, revised 1996). Under sterile, anesthetized conditions (30 mg/kg iv pentobarbital sodium), a group of animals was prepared as a 1K1C renal hypertensive model (4, 20, 27). A left-flank incision exposed the left kidney, and the renal artery was dissected free. A Sterling-silver clip (0.5-mm gap opening) was threaded around the artery and folded over itself, securing it in place. The incision was closed, and the contralateral kidney was then exposed. The ureter, renal artery, and vein were ligated, and the kidney was excised. Animals were allowed to recover for 35 days.

In the terminal experiments, 24 1K1C and 24 control animals were used. All animals were anesthetized with pentobarbital sodium (30 mg/kg) in the circumflex ear vein, and this was supplemented as needed. A saline-filled catheter was inserted in a femoral artery for measurement of systemic arterial blood pressure for withdrawal of blood for blood flow measurements and for the anaerobic acquisition of samples for blood gas analysis. The venous cannula was used for administration of Prop and additional anesthetic. A tracheostomy was performed, and an endotracheal tube was inserted to allow for artificial respiration with a Harvard respirator. A left-sided thoracotomy was performed at the fourth intercostal space, and a pericardial cradle was created. An intra-atrial cannula was inserted to allow injection of radioactive microspheres for calculation of myocardial blood flow and cardiac output. Myocardial wall thickness and its maximal rate of change (dW/dtmax) were measured by an ultrasonic crystal sutured to the surface of the left ventricle (Crystal Biotech). Left ventricular pressure and its maximal rate of development (dP/dtmax) were achieved through the insertion of a Millar pressure-tipped probe into the left ventricle via a stab wound near the apex. This data-acquisition system was used to record the following parameters continuously and simultaneously: heart rate, aortic blood pressure, left ventricular blood pressure, dP/dtmax, left-ventricular wall thickening, and dW/dtmax. Arterial blood gases were measured with a Radiometer ABL 330 blood-gas analyzer, and tidal volume, ventilation rate, and inspired O2 fraction were adjusted as needed to maintain physiological parameters (arterial PO2 of >80 Torr, arterial PCO2 of 30–40 Torr).

Experimental protocol. After the surgical preparation was completed, animals were allowed to stabilize for 15 min, after which arterial blood gases, heart rate, blood pressures, dP/dtmax, and wall-thickening parameters were measured in preparation for a control coronary blood flow measurement. A dose of ∼5 × 105 of either 141Ce- or 95Nb-labeled microspheres was agitated for ∼2 min and then slowly injected as a 0.2-ml bolus into the atrial catheter, which was then flushed with 1 ml of saline over the next 20 s. A 3-min timed-reference blood sample, beginning 30 s before the injection of radioactive microspheres, was obtained from the femoral artery with a pump set at 2 ml/min. No changes in hemodynamic parameters occurred during this procedure. The reference-sample method was used to calculate the coronary blood flow of the left-ventricular free wall.

Both control and 1K1C animals were divided into four groups: control, 8-Br-cGMP (10−3 M), Prop (2 mg/kg iv), and Prop + 8-Br-cGMP. In the groups given Prop, this agent was injected into the venous catheter 15 min before final measurements. A cotton gauze sponge soaked with either vehicle (10% ethanol in 0.9% saline) or 8-Br-cGMP (10−3 M) was applied to the left-ventricular epicardial surface, and measurements were obtained after 10 min. Previous work from our laboratory had demonstrated good delivery of agents to the full thickness (∼2.5 mm) of the rabbit left-ventricular free wall (9, 20, 22). Blood pressures, heart rate, and wall thickening were again monitored continuously during this period, after which arterial blood gases were measured. Coronary blood flow was determined with an alternatively labeled radioactive nuclide. The hearts were then excised at the atrioventricular ring and frozen in liquid nitrogen.

Regional coronary blood flow, O2 extraction, and O2 consumption. Hearts were weighed, and the left-ventricular free wall was removed with a band saw at −20°C. We divided the free wall into an inner subendocardial (Endo) and an outer subepicardial (Epi) half using a straight-edged razor blade on dry ice. Sections were then weighed and kept frozen on dry ice until blood flow was determined. The activity of the radioactive microspheres in each blood and tissue sample was determined with a Hewlett-Packard Auto Gamma Spectrometer. Arterial blood samples obtained from the timed-reference samples were weighed and placed in the spectrometer along with the tissue samples. The tissue samples were kept on dry ice and placed in the gamma counter singly, for 1 min each, to ensure they remained frozen. No visible thawing occurred during this time period. Blood flows were calculated from the formula Fu = Fk(Cu/Ck), where Fu is the flow to any organ, Fk is the flow to the reference organ, Cu is the radioactivity in any organ, and Ck is the radioactivity in the reference organ. Myocardial blood flow was expressed in milliliters per minute per 100 g of tissue. Cardiac output was determined with the equation cardiac output = Fk(Cy/Cy), where Cy is the radioactivity in the injected dose of microspheres.

Arterial and venous O2 saturations were determined from samples of the left ventricular free wall of each heart. Details of this technique have been published previously (31). Briefly, the regions were mounted with an embedding medium in a microtome-cryostat. Twenty micra sections were obtained on the microtome-cryostat at −35°C under a N2 atmosphere. The sections were transferred to precooled glass slides and covered with degassed silicone oil and a coverslip. These slides were placed on a microspectrophotometer fitted with a N2-flushed cold stage to obtain readings of optical density at 568, 560, and 523 nm. This three-wavelength method corrects for the light scattering in the frozen blood. Readings were obtained to determine O2 saturation in five arteries and seven veins. The O2 content of blood was determined by multiplying the percent O2 saturation by the hemoglobin concentration times 1.36 ml O2/g. The difference between the average myocardial arterial and venous O2 contents (regional O2 extraction) was then obtained. With the use of the Fick principle, the paired product of local O2 extraction and blood flow was used to determine myocardial O2 consumption. Myocardial cAMP levels. To determine cAMP levels, tissue samples were warmed to 0°C and homogenized in ethanol with a Brinkman Polytron in an ice bath. The homogenate was centrifuged at 30,000 g for 15 min in a Sorvall RC-5B centrifuge. The supernatant was recovered. The pellet was resuspended in 1 ml of 2:1 ethanol-water solution and centrifuged as before. The combined supernatants were evaporated to dryness in a 60°C bath under a stream of nitrogen gas. The final residue was dissolved in 1.5 ml of assay buffer (0.05 M sodium acetate, pH 5.8, containing sodium azide). cAMP levels were determined with a radioimmunoassay (Amersham). This assay measures the competitive binding of 125I-labeled cAMP to a cAMP-specific antibody. After construction of a standard curve, cAMP levels were determined directly from the counts in picomoles per gram of tissue wet weight.

Statistical analysis. A repeated-measure ANOVA was used to determine whether there were differences in hemodynamic or blood-gas variables between treatments and groups. This analysis was also used to determine differences between regions, groups, and treatments for myocardial O2 consumption, cardiac function, cGMP, and coronary blood flow indexes. Duncan’s post hoc procedure was used to assess differences between means.
ventricular dP/dt max (t/H11001 pressure (t/H11001 cannot. All values are expressed as means 

Table 2. Arterial blood gas data in control rabbits and those with 1K1C renal hypertension with vehicle, 8-Br-cGMP, Prop, and 8-Br-cGMP + Prop

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>8-Br-cGMP</th>
<th>Prop</th>
<th>8-Br-cGMP + Prop</th>
<th>Vehicle</th>
<th>8-Br-cGMP</th>
<th>Prop</th>
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<tr>
<td>Pre</td>
<td>7.34 ± 0.04</td>
<td>7.29 ± 0.02</td>
<td>7.31 ± 0.02</td>
<td>7.37 ± 0.02</td>
<td>7.39 ± 0.03</td>
<td>7.35 ± 0.05</td>
<td>7.36 ± 0.03</td>
<td>7.34 ± 0.02</td>
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<tr>
<td>Post</td>
<td>7.31 ± 0.03</td>
<td>7.33 ± 0.01</td>
<td>7.33 ± 0.02</td>
<td>7.33 ± 0.02</td>
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<td>Po2, Torr</td>
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<tr>
<td>Pre</td>
<td>118 ± 10</td>
<td>120 ± 10</td>
<td>111 ± 10</td>
<td>129 ± 9</td>
<td>140 ± 25</td>
<td>138 ± 15</td>
<td>136 ± 14</td>
<td>114 ± 16</td>
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<tr>
<td>Post</td>
<td>110 ± 17</td>
<td>125 ± 7</td>
<td>136 ± 9</td>
<td>127 ± 9</td>
<td>131 ± 22</td>
<td>136 ± 13</td>
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<td>PCO2, Torr</td>
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<td></td>
</tr>
<tr>
<td>Pre</td>
<td>32 ± 2</td>
<td>35 ± 2</td>
<td>41 ± 1</td>
<td>33 ± 2</td>
<td>35 ± 3</td>
<td>34 ± 2</td>
<td>33 ± 1</td>
<td>30 ± 2</td>
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<tr>
<td>Post</td>
<td>37 ± 2</td>
<td>34 ± 2</td>
<td>38 ± 3</td>
<td>36 ± 2</td>
<td>39 ± 3</td>
<td>34 ± 3</td>
<td>37 ± 2</td>
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Values are means ± SE.

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the significance of differences. In all cases, a value of P < 0.05 was accepted as significant. All values are expressed as means ± SE.

RESULTS

The 1K1C rabbits had significantly greater heart weights (8.00 ± 0.21 g in 1K1C vs. 6.68 ± 0.20 g in control), although no significant difference was seen in the heart weight-to-body weight ratios (2.80 ± 0.18 for 1K1C vs. 2.74 ± 0.23 for control) between 1K1C and control rabbits. Global hemodynamic and myocardial functional data before and after treatment with vehicle, 8-Br-cGMP, Prop, or Prop + 8-Br-cGMP for the two groups are presented in Table 1. In the 1K1C animals, initial systolic blood pressure (+23%), diastolic blood pressure (+24%), mean arterial pressure (+23%), and left ventricular dP/dt max (+32%) were significantly increased compared with that of the vehicle-treated control animals. In 1K1C animals, heart rate, left ventricular dP/dt max, and dW/dt max were not significantly different from the control group after treatment with the various agents employed at the time of the final measurement.

In the control group, no significant differences were seen in blood pressure, left ventricular dP/dt max and dW/dt max, heart rate, and cardiac output after treatment with 8-Br-cGMP. Also, after treatment with Prop, no differences were seen except for a fall in heart rate and left ventricular dP/dt max. After treatment with Prop + 8-Br-cGMP, significant falls in left ventricular dP/dt max and dW/dt max and heart rate was observed. In the 1K1C group, no significant differences were seen in blood pressure, left ventricular dP/dt max and dW/dt max, heart rate, and cardiac output after treatment with 8-Br-cGMP. After treatment with Prop, there were significant falls in blood pressure, heart rate, left ventricular dP/dt max, dW/dt max, and cardiac output. After treatment with Prop + 8-Br-cGMP, left ventricular dP/dt max and heart rate fell. The arterial blood-gas data are shown in Table 2. No significant differences occurred during any treatment in either control or 1K1C rabbits in pH, Po2, and PCO2.

Coronary blood flow data are presented in Table 3. There were no significant Epi vs. Endo differences in blood flow during any treatment in either control or 1K1C animals. In the control group, no significant differences were seen in coronary blood flow during any treatment, except that blood flow was lower in the Endo region of the Prop + 8-Br-cGMP group compared with vehicle. The 1K1C animals did not have coronary blood flows that differed significantly from the control group. In the 1K1C Prop and 8-Br-cGMP treatment groups, coronary blood flow in both the Epi and Endo were significantly reduced compared with the vehicle-treated 1K1C group.

Myocardial O2 extraction data are also presented in Table 3. There were no significant Epi vs. Endo differences in myocardial O2 extraction in either control or 1K1C rabbits. In the control group, no significant differences were seen in myocardial O2 extraction during any treatment. In the 1K1C group, a significant difference was seen in myocardial O2 extraction between the control and 1K1C groups after treatment with Prop + 8-Br-cGMP.
dial O\textsubscript{2} extraction during any treatment in either the control or 1K1C animals. In the control group, no significant differences were seen in myocardial O\textsubscript{2} extraction during any treatment, except that O\textsubscript{2} extraction was higher in the Endo region of the Prop/H\textsubscript{11001}8-Br-cGMP group compared with vehicle. In the Epi and Endo of the vehicle-treated group and the Endo of the Prop group, 1K1C animals had significantly higher myocardial O\textsubscript{2} extractions than the comparable group in the controls. There were no significant differences in myocardial O\textsubscript{2} extraction between any treatment groups in the 1K1C rabbits.

Myocardial O\textsubscript{2} consumption of the Epi and Endo regions of the left ventricular free wall in the control and 1K1C rabbits are shown in Fig. 1. There were no statistically significant differences between control and 1K1C rabbit hearts, nor were there any Epi vs. Endo differences. In the control group, 8-Br-cGMP failed to significantly alter myocardial O\textsubscript{2} consumption. After

### Table 3. Regional coronary blood flow and oxygen extraction in control rabbits and 1K1C rabbits with vehicle, 8-Br-cGMP, Prop, and 8-Br-cGMP + Prop

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypertension</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Prop</td>
</tr>
<tr>
<td>Coronary blood flow, ml\textsuperscript{-1} min\textsuperscript{-1} 100 g\textsuperscript{-1}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>132±19</td>
<td>148±21</td>
</tr>
<tr>
<td>Endo</td>
<td>143±14</td>
<td>160±10</td>
</tr>
<tr>
<td>Myocardial oxygen extraction, ml O\textsubscript{2}/100 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epi</td>
<td>6.9±0.2</td>
<td>6.4±0.3</td>
</tr>
<tr>
<td>Endo</td>
<td>6.7±0.3</td>
<td>6.5±0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. Epi, subepicardial; Endo, subendocardial. *Significantly different from vehicle. †Significantly different from comparable control group.
treatment with Prop, a significant decrease was seen in myocardial O$_2$ consumption in both the Epi and Endo compared with vehicle. A similar significant decrease in myocardial O$_2$ consumption was also observed in the Prop + 8-Br-cGMP group compared with vehicle. In the 1K1C group, all treatments significantly lowered myocardial O$_2$ consumption compared with vehicle treatment. These decrements were observed in both the Epi and Endo regions after 8-Br-cGMP, Prop, and Prop + 8-Br-cGMP (Fig. 1).

Figure 2 shows the regional cAMP levels measured in the Epi and Endo of the control and 1K1C rabbit hearts. There were no statistically significant differences in the level of cAMP between the control and 1K1C groups with regard to any region or treatment. Treatment with 8-Br-cGMP alone had no significant effect on the level of cAMP in control or 1K1C hearts. There were significant decreases in cAMP levels after Prop and Prop + 8-Br-cGMP treatment in both control and hypertensive rabbits. These changes were observed in both the Epi and Endo regions of the left ventricular free wall on the control and 1K1C rabbits. No other significant changes in cAMP were noted.

DISCUSSION

The purpose of the present study was to test the hypothesis that decreasing concentrations of cAMP with Prop, a β-adrenergic blocking agent, while simultaneously increasing myocardial cGMP, would result in a potentiation of their negative inotropic and metabolic effects, and this would lower coronary flow. We also sought to determine whether this relationship would be altered in the presence of renal hypertension. We found that, under control conditions, only Prop, not 8-Br-cGMP, lowered O$_2$ consumption of the rabbit heart and that there was no additive effect. In a 1K1C renal hypertension condition, both Prop and 8-Br-cGMP lowered myocardial O$_2$ consumption. However, there was also no additive effect. The combination did lower coronary flow. In addition, in both control and 1K1C hearts, only Prop affected the myocardial level of cAMP, indicating a lack of in vivo effects of the second-messenger cGMP on the level of cAMP. These effects were transmural in the left ventricular free wall with no Epi vs. Endo differences.

It has been shown that significant positive inotropic and metabolic effects in the heart can be achieved by stimulating...
cAMP synthesis or by inhibiting cAMP degradation (8, 15, 18). These effects are largely related to activation of the cAMP-dependent protein kinase and increases in the cytosolic level of calcium (15, 18, 26). β-Adrenergic blockade with Prop lowered the myocardial level of cAMP and reduced myocardial O₂ consumption in the control rabbit hearts. This is one of the useful clinical characteristic of β-adrenergic blocking agents (21). There must have been a significant level of β-adrenergic activation in these control rabbits hearts for this decrease in metabolism to occur.

Nitric oxide and its second messenger cGMP have negative metabolic and functional effects in both the myocardium and isolated cardiac myocytes in many species (5, 14, 17, 24, 28). They can cause reductions in local metabolism, force development, inotropy, and contractile duration (10, 14, 20, 23). These effects operate through protein nitrosylation by nitric oxide, phosphorylation by cGMP-dependent protein kinase, cGMP-regulated cAMP phosphodiesterases, and direct inhibition of L-type calcium channels (5, 25). It had been suggested that inhibition of L-type calcium channels by cGMP acted through the cGMP-dependent protein kinase (5, 13, 25). It is not clear which is the predominant mechanism in the rabbit. We found that the addition of a cell-permeable form of cGMP had no significant effect on O₂ consumption, function, or the level of cAMP in the rabbit heart. This is in contrast to other studies where there was a fall in myocardial O₂ consumption after increases in the endogenous levels of cGMP using nitric oxide or cGMP phosphodiesterase inhibitors (6, 20, 30). It is not clear why 8-Br-cGMP did not lower local O₂ consumption, although there are some reports that low doses of cGMP or nitric oxide may be stimulatory (14, 23, 28). This could be related to effects on the cGMP-inhibited cAMP phosphodiesterase leading to increases in cAMP (16). This form of cGMP had been shown to affect cardiac function, but not O₂ consumption, during myocardial stunning in rabbit heart (9). Previous studies had demonstrated adequate delivery of substances by epicardial suffusion (9, 20, 22).

Nitric oxide and cGMP can cause direct vasodilatation (3, 17, 25). However, because they can also lower cardiac metabolism, we saw little change in coronary blood flow (6, 20, 30). cGMP can affect the level of cAMP through its actions on the cGMP-stimulated and cGMP-inhibited cAMP phosphodiesterases (14, 16, 18, 23, 29). These effects may limit or enhance the functional and metabolic effects of cAMP depending on which cGMP-affected cAMP phosphodiesterase is more affected (16, 29). In the present study, we found no functional effect of cGMP with regard to its interaction with cAMP in control hearts. In addition, cGMP did not alter the level of cAMP. Prop lowered myocardial metabolism and cAMP levels. The addition of 8-Br-cGMP did not further alter the level of cAMP or myocardial O₂ consumption but did lower Endo blood flow. This may be related to the fact that Prop lowered the myocardial level of cAMP, and, therefore, changes in the activity of the cAMP phosphodiesterases had small effects on the heart.

Renovascular hypertension can produce major changes in the heart (11). These changes can be related to alterations in structure, metabolism, function, and signal transduction (4, 20, 22, 27). Major regulators of arterial blood pressure involve the adrenergic nervous system and nitric oxide production (1, 3, 7, 19). Hypertension can lead to alterations in myocardial signal transduction, especially in the nitric oxide and β-adrenergic signal transduction systems (1, 3). It has been reported that there are alterations in the cardiac and myocyte responses to changes in the level of the second messenger cAMP and cGMP in renal hypertensive rabbits (4, 16, 20, 27). Our renal hypertensive model (1K1C) led to significant increases in aortic blood pressure. The baseline structural, functional, and metabolic values for the heart, however, were very similar to the control rabbits. The heart weight-to-body weight ratio was not significantly different. Myocardial O₂ consumption, coronary blood flow, wall motion, and cAMP levels in the 1K1C rabbits were also similar to those in the control group. Renal hypertension did not cause significant Epi vs. Endo effects in the left ventricular free wall.

Prop administration lowered both myocardial O₂ consumption and cAMP levels in the 1K1C rabbit hearts in a manner similar to its effects in the control hearts. β-Adrenergic blocking agents have been successfully used for the treatment of hypertension (7, 20). There were no significant differences in the myocardial effects of β-adrenergic blockade between control and hypertensive hearts. Chronic treatment with β-adrenergic blockade has been found to have a beneficial effect on the heart in renal hypertension in this model (4). Hypertension can affect the functioning and signal pathway of the β-adrenergic system (2, 7), but in our model of renal hypertension the effects of blockade of this system were similar to control.

The present findings demonstrated that increasing the endogenous basal level of the second-messenger cGMP in the heart decreased myocardial O₂ consumption during renal hypertension, although no significant effect was seen in the control rabbit hearts. This was without a significant decrease in coronary blood flow. Previous evidence demonstrated alterations in the relationship between the myocardial level of cGMP and O₂ consumption in the rabbit heart during renal hypertension (16, 20, 22). Differential myocardial responses to cGMP during hypertension may be related to changes in cardiac structure or function or changes in the signaling pathway (3, 16, 22, 23). The degree of metabolic decrement in the 1K1C hearts with 8-Br-cGMP was similar to that observed with Prop, although coronary flow decreased with Prop.

In our experiments, the results demonstrated no further decrement in myocardial O₂ consumption for the group with the combination of 8-Br-cGMP and Prop compared with either treatment alone in the 1K1C heart. This evidence suggested that some common mechanism was activated, e.g., calcium release or reuptake, and was not further affected by additional stimulation. Many studies have demonstrated that cGMP can affect the level of cAMP through its effects on cGMP-stimulated and cGMP-inhibited cAMP phosphodiesterases (14, 16, 18, 23, 29). These effects may not be that important when the level of cAMP is lowered by Prop. In the 1K1C model, both decreasing cAMP and increasing cGMP significantly reduced myocardial O₂ consumption, but this effect was not additive. The combination did lower coronary blood flow. Although renal hypertension increased the negative metabolism effects of cGMP, the effects of cAMP and its interaction with cGMP were not affected. It is not clear which of the mechanisms for actions of cGMP and cAMP on the heart could be altered in the 1K1C model, therefore altering the balance-counter balance relationship between the second messengers cAMP and cGMP.
In summary, in the control rabbit heart, only Prop lowered myocardial O₂ consumption, and there was no additive effect of increasing the level of cGMP. In 1K1C renal hypertension, both Prop and 8-Br-cGMP lowered myocardial O₂ consumption. However, there was also no additive metabolic effect. Coronary blood flow was decreased by the combination. In addition, in both control and 1K1C hearts, only Prop affected coronary blood flow. However, there was also no additive metabolic effect. The effects of the second messenger cGMP on the level of cAMP addition, in both control and 1K1C hearts, only Prop affected myocardial level of cAMP, indicating a lack of in vivo effects of the second messenger cGMP on the level of cAMP after the myocardial level of cAMP was lowered. These data suggest some change in myocardial signal transduction during renal hypertension.

REFERENCES

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