Attenuation of Vasopressin-Mediated Coronary Constriction and Myocardial Depression in the Hypoxic Heart

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To investigate the ability of arginine vasopressin (AVP) to compete with metabolic vasodilatory factors in the coronary circulation, we examined the coronary vascular and myocardial effects of AVP in isolated working rat hearts during normoxic and hypoxic perfusion. In normoxic hearts, AVP treatment (777±67 pg/ml) reduced coronary flow by 38.4±2.6%. Myocardial function was also significantly decreased by AVP whereas efficiency significantly increased. In contrast, the same dose of AVP administered to hypoxic hearts resulted in substantially smaller effects on coronary flow (−11.5±2.8%), myocardial function, and efficiency. In hearts treated first with AVP and then with hypoxia, the greater degree of coronary vasodilation compared with that observed in hearts treated with hypoxia alone also indicated an antagonizing effect of hypoxia on AVP-mediated coronary constriction. It was also noted that the hypoxia treatment alone resulted in reductions of O₂ supply and consumption identical to those produced by AVP treatment during normoxia. However, hypoxia was associated with a significantly greater effect on myocardial function and, in contrast to the effect of AVP, a marked reduction in efficiency. The rate of lactate release was greater during hypoxia alone (2.07±0.08 μmol/min) than with AVP treatment during normoxia (0.76±0.05 μmol/min). These results indicate that the effect of AVP on the coronary vessels, as well as its effect on the myocardium, is significantly attenuated during hypoxia. In addition, AVP-constricted vessels appear to retain considerable vasodilatory reserve despite evidence of ischemic conditions. Thus, although the effects of AVP resemble ischemia, the increased efficiency and the relatively small effect of AVP on contractile function, as well as the preserved vasodilatory reserve, suggest otherwise. A physiological explanation for these observations is proposed wherein the constricting effects of AVP modulate the effects of autoregulatory factors such that blood flow requirements are minimized while allowing preservation of adequate blood flow for vital tissue function. (Circulation Research 1990;66:710–721)

Numerous studies indicate that arginine vasopressin (AVP) is a potent coronary constricting agent capable of producing a myocardial ischemia–like state characterized by coronary venous O₂ desaturation, increased myocardial lactate production, tissue lactate accumulation, and depressed myocardial function.¹–⁴

Although it has been suggested that the coronary constriction attributed to AVP may be secondary to baroreflex-mediated decreases in myocardial oxygen demand,⁵ infusion of AVP into coronary arteries or administration to isolated cardiac preparations results in substantial reductions in coronary flow in the absence of such reflex effects or changes in the hemodynamic determinants of oxygen demand or coronary perfusion.¹–⁴ Coronary constriction might also result from AVP-induced direct myocardial depression.⁶–¹⁰ However, the coronary venous O₂ desaturation and increased myocardial lactate production that accompany the coronary flow decrease¹–⁴ are inconsistent with coronary constriction secondary to myocardial depression and suggest, rather, that the depressed contractile function observed is the result of AVP-induced ischemia.¹,⁴,¹¹ Reports of ischemic electrocardiographic changes¹² and myocardial infarction after AVP treatment¹³–¹⁵ further attest to the potential for AVP to produce myocardial ischemia.

The physiological importance of the direct cardiac effects of AVP are suggested by the recent demonstration that dose-dependent coronary constriction,
myocardial depression, and increased lactate release occur at AVP concentrations that are observed during AVP release in vivo. Considerable evidence indicates that such AVP release in vivo can produce direct constriction of systemic vessels, and these recent results further indicate that direct coronary constriction occurs over the same concentration range (10−1,000 pg/ml).

Although the systemic vasoconstriction produced by endogenous AVP appears to be important in blood pressure maintenance, the coronary constriction produced by AVP would appear to offer no homeostatic advantage. The fact that AVP-mediated coronary constriction can result in myocardial ischemia, and that such constriction persists in spite of marked reductions of coronary perfusion pressure, suggests that autoregulatory factors may not be able to effectively compete with AVP for control of the coronary circulation. Thus, the massive AVP release that occurs in response to hemorrhage, hypotension, and hypoxia could result in further compromise of an already limited myocardial oxygen supply. Furthermore, although the ability of endogenously released AVP to produce myocardial ischemia and infarction has not been demonstrated, considerably elevated plasma levels of AVP have been reported in patients with evolving myocardial infarctions. If metabolic autoregulatory factors cannot compete with AVP despite intense vasodilatory stimuli, endogenous AVP may worsen ischemia in such patients by constricting the dilated vascular bed distal to a coronary artery stenotic lesion.

The present study was undertaken to establish the extent to which physiologically relevant amounts of AVP compete with metabolic vasodilatory factors for control of the coronary circulation. An isolated working rat heart preparation was used to study the cardiac effects of AVP treatment on normoxic hearts and hearts in which metabolic vasodilation was maximized by lowering the oxygen content of the perfusing medium (i.e., “hypoxia”). We also compared the cardiac response to the hypoxia treatment in AVP-treated and untreated hearts. In addition, both the hypoxia and AVP treatments chosen produced similar reductions in myocardial oxygen delivery and consumption, allowing a further comparison of the effects of myocardial hypoxia to those of AVP-mediated myocardial “ischemia.” The isolated heart model is ideally suited for such a study since direct cardiac effects can be evaluated in the absence of reflex effects or systemic hemodynamic effects that can indirectly influence myocardial oxygen supply or demand and/or myocardial performance in vivo. In addition, myocardial hypoxia could be produced and controlled easily in this model by lowering the oxygen content of the perfusion medium.

Materials and Methods

The animal preparation and perfusion techniques were similar to those described previously. In brief, male Long-Evans hooded rats were housed individually with ad libitum Purina lab chow and water until the experiment. Hearts were removed from heparinized (1,000 units/kg i.p.) rats that were anesthetized with sodium pentobarbital (60 mg/kg i.p.). The hearts were then attached to the aortic cannula of the perfusion apparatus, and retrograde perfusion was begun (60 mm Hg perfusion pressure). The left ventricle (LV) was cannulated by inserting a flanged cannula through the mitral valve, piercing the LV apex, and seating the flange against the endocardial wall. The LV cannula was connected to a pressure transducer to obtain LV pressure indexes. The pulmonary veins were ligated to another flanged cannula connected to the left atrial reservoir, and working-heart (“antegrade”) perfusion was then begun. Perfsurate entered the LV via the left atrium and exited via the aorta. The left atrial filling pressure was maintained at 10 cm hydrostatic pressure; coronary perfusion pressure was maintained at 55 mm Hg hydrostatic pressure. After antegrade perfusion was initiated, the hearts were allowed to equilibrate for 10 minutes at spontaneous heart rates. This equilibration period was followed by right atrial pacing at 325 beats/min and by another equilibration period before measurements were made of initial (baseline) cardiac parameters.

The perfusate had the following electrolyte composition (mM): Na+ 146, K+ 6.3, Ca2+ 2.85, Mg2+ 1.36, H2PO4− 1.36, Cl− 134, HCO3− 22.6, glucose 11.1, and EDTA 0.45. Perfsurate was equilibrated with normoxic gas mixture (95% O2−5% CO2) throughout the experiment (Pao2, 626±2 mm Hg) except for the period of hypoxia treatment, during which 50% O2−5% CO2−45% N2 was used (Pao2, 383±3 mm Hg).

LV systolic pressure, peak rates of LV pressure rise (dP/dt) and relaxation (−dP/dt), and LV enddiastolic pressure (LVEDP) were measured via the LV cannula. Aortic output was measured by collecting the overflow from the aortic reservoir; aortic flow rate was measured by a cannulating flow transducer in the proximal aorta. Coronary flow was measured by collecting the effluent from the right side of the heart, which exited via the pulmonary artery into a pressure/volume device below the heart. Total cardiac output was taken to be equal to aortic output plus coronary flow.

Arterial and venous PO2 values were obtained by withdrawing perfusate samples from the left atrial reservoir and the pulmonary artery, respectively, via polyethylene cannulas that were directly connected to a thermoregulated chamber containing a Clark O2 electrode (models D616 and E5046, Radiometer America, Westlake, Ohio).

The pressure, coronary flow, and aortic flow rate data were collected and stored on-line for later analysis using a PDP 11/23 minicomputer. Myocardial oxygen consumption (MVO2), power, stroke work, and external work efficiency were computed from the measured parameters as previously described:

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MVO₂ (ml O₂/min g DHW) =
(3.210×10⁻⁵ ml O₂/ml perfuse mm Hg) ×
(PaO₂ - PVO₂) × CF/DHW

Power(t) (ergs/sec g DHW) =
(1,333 dyne/cm² mm Hg) × LVSP(t) × AF(t)/DHW

Stroke work (ergs/g DHW) =
Power(t)/dt (during ejection)

External work efficiency (%) =
(4.684×10⁻⁷ ml O₂/erg) × Stroke work/MVO₂
× HR × 100

Efficiency was calculated assuming that O₂ was used entirely for the oxidation of glucose²⁶; PaO₂ and PVO₂, arterial and venous O₂, respectively (mm Hg); CF, coronary flow (ml/min); t, time (sec); DHW, dry heart weight (g); LVSP, LV systolic pressure (mm Hg); AF, aortic flow rate (ml/sec); and HR, heart rate (hearts/min). Myocardial O₂ supply was calculated as coronary flow times the difference between the arterial O₂ content and the O₂ content of maximally extracted coronary venous perfusate. A perfusate sample was taken at each measurement point for lactate assay.²⁷

At the conclusion of the experiment the left and right ventricles were dried at 110°C for 16 hours to obtain a dry weight.

Pharmacological Agents

Synthetic AVP (Pitressin, Parke-Davis, Morris Plains, New Jersey) was diluted in saline immediately before use. In AVP-treated hearts, AVP was added to the perfusate to produce a final concentration of approximately 1,000 pg/ml. The AVP concentration used was similar to the plasma levels reported during severe hemorrhage or hypotension²³ and produced a maximal effect on coronary flow in the isolated heart model.¹ Perfusate samples were taken each time cardiac parameters were measured to determine the exact concentrations of AVP by radioimmunooassay.¹

The AVP vascular antagonist [1-(β-mercaptoprotyl-β,β-cyclopentamethylene-propionic acid),2-(O-methyl)tyrosine]arginine-vasopressin (Manning compound; d(CH₂)₅ tyr(Me)AVP)²₈ was purchased from Bachem, Torrance, California. A 1.0 mg/ml stock solution was prepared in 0.2N acetic acid and was further diluted in saline immediately before use. The dose of antagonist (20 ng/ml of perfusate) used in these experiments was previously found to reverse all the cardiac effects of AVP at the concentration studied.¹

Experimental Design

After initial cardiac parameter measurements were made, the hearts were studied using one of the following protocols (n = 6 hearts per group): AVP during normoxia (group 1). 1) AVP was added to the perfusate, and after a 10-minute stabilization period, “prehypoxia” measurements were made. 2) The perfusate equilibration gas was then changed from the normoxic (95% O₂) to the hypoxic (50% O₂) mixture, and after stabilization (15 minutes), “hypoxia 1” measurements were made. 3) After another 15-minute period of hypoxic perfusion, “hypoxia 2” measurements were made. 4) The equilibration gas was then changed back to the normoxic gas mixture, and after a 15-minute stabilization period, “posthypoxia 1” measurements were made. 5) The AVP antagonist was then added to the perfusate (20 ng/ml), and after a 10-minute stabilization period, “posthypoxia 2” measurements were made. AVP during hypoxia (group 2). The protocol was identical to that for group 1, except AVP was added to the perfusate after the hypoxia 1 measurements rather than after baseline measurements. Hypoxia alone (group 3). The same protocol was followed as for groups 1 and 2 except there was no treatment with AVP. Normoxia control (group 4). The same protocol was followed as in groups 1–3 with respect to the timing of the cardiac parameter measurements, but there was neither AVP treatment nor hypoxia treatment (i.e., normoxic gas mixture was used throughout).

Data Analyses

All data are reported as mean±SEM. Initial cardiac parameters, animal body weights, heart dry weights, duration of hypoxia, normoxia PaO₂, and hypoxia PaO₂ were analyzed using one-way analysis of variance to evaluate differences among the groups. Cardiac parameter measurements (except for LVEDP and lactate data) obtained subsequent to the initial measurement were converted to percent of initial value and were analyzed using two-way analysis of variance with repeated measures. A one-way analysis of variance and Tukey’s test were then used to identify significant group differences at the various time points. The perfusate AVP levels in the two AVP-treated groups (groups 1 and 2) were analyzed similarly. The effects of AVP treatment during normoxia versus AVP treatment during hypoxia were also analyzed with a two-way analysis of variance and Tukey’s test in which responses in the AVP-treated hearts (normoxia+AVP and hypoxia+AVP) and the control hearts (normoxia control and hypoxia control) were compared. The effects of AVP treatment alone versus hypoxia treatment alone were compared by Student’s paired t test. Differences were considered significant when p<0.05.

Results

The initial cardiac parameters and the animal and heart weights for the four groups of hearts are shown in Table 1. There were no significant differences among the groups for any of these values, which are comparable with values previously reported for this model.¹,²⁴,²⁵ The perfusate AVP levels for groups 1 and 2 are shown in Table 2. There was no significant difference in perfusate AVP concentrations between groups 1 and 2. In addition, there were no significant effects of time on perfusate AVP concentration in
TABLE 1.  Initial Cardiac Parameters and Rat and Heart Weights

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP_{max} (mm Hg)</td>
<td>111.1±1.4</td>
<td>109.9±2.5</td>
<td>105.9±1.2</td>
<td>108.3±1.3</td>
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<tr>
<td>dP/dt_{max} (mm Hg/sec)</td>
<td>4,386±247</td>
<td>4,405±209</td>
<td>4,030±131</td>
<td>4,107±127</td>
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<tr>
<td>−dP/dt_{max} (mm Hg/sec)</td>
<td>3,411±48</td>
<td>3,490±87</td>
<td>3,201±141</td>
<td>3,306±185</td>
</tr>
<tr>
<td>AF rate_{max} (ml/min)</td>
<td>276.1±4.1</td>
<td>274.1±6.6</td>
<td>257.8±2.3</td>
<td>278.0±6.2</td>
</tr>
<tr>
<td>Stroke work×10^{-6} (ergs/g DHW)</td>
<td>0.125±0.003</td>
<td>0.119±0.008</td>
<td>0.113±0.006</td>
<td>0.125±0.006</td>
</tr>
<tr>
<td>Power_{max}×10^{-7} (ergs/sec g DHW)</td>
<td>0.303±0.008</td>
<td>0.288±0.020</td>
<td>0.273±0.014</td>
<td>0.298±0.014</td>
</tr>
<tr>
<td>LVSP_{mar},,, (mm Hg)</td>
<td>97.8±1.3</td>
<td>97.8±1.3</td>
<td>97.8±1.3</td>
<td>97.8±1.3</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>210±7</td>
<td>200±7</td>
<td>190±7</td>
<td>178±11</td>
</tr>
<tr>
<td>Aortic output (ml/min g DHW)</td>
<td>353.9±6.5</td>
<td>337.5±17.8</td>
<td>329.4±19.3</td>
<td>359.0±16.1</td>
</tr>
<tr>
<td>Cardiac output (ml/min g DHW)</td>
<td>364.3±7.0</td>
<td>346.4±18.1</td>
<td>343.7±21.9</td>
<td>364.2±13.7</td>
</tr>
<tr>
<td>MVo2 (ml/min g DHW)</td>
<td>1.11±0.03</td>
<td>1.10±0.06</td>
<td>1.09±0.02</td>
<td>1.16±0.04</td>
</tr>
<tr>
<td>Efficiency (%)</td>
<td>17.3±0.4</td>
<td>16.6±0.8</td>
<td>15.9±0.5</td>
<td>16.5±0.6</td>
</tr>
<tr>
<td>Venous Po2 (mm Hg)</td>
<td>204±12</td>
<td>190±7</td>
<td>200±7</td>
<td>178±11</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>3.7±0.3</td>
<td>3.5±0.4</td>
<td>3.1±0.4</td>
<td>3.5±0.3</td>
</tr>
<tr>
<td>Lactate release (umol/min g DHW)</td>
<td>2.94±0.42</td>
<td>2.00±0.33</td>
<td>2.57±0.31</td>
<td>2.21±0.50</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>383±7</td>
<td>377±12</td>
<td>363±17</td>
<td>400±25</td>
</tr>
<tr>
<td>DHW (mg)</td>
<td>184.1±3.6</td>
<td>194.0±7.7</td>
<td>187.4±9.2</td>
<td>186.2±10.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. For all groups, n=6. Group 1, arginine vasopressin during normoxia; group 2, arginine vasopressin during hypoxia; group 3, hypoxia alone; group 4, normoxia control; LVSP_{max}, left ventricular peak systolic pressure; dP/dt_{max} and −dP/dt_{max}, peak rates of left ventricular pressure rise and relaxation, respectively; AF rate_{max}, peak aortic flow rate; DHW, dry heart weight; Power_{max}, peak power; MVo2, myocardial oxygen consumption; LVEDP, left ventricular end-diastolic pressure.

either group, which indicated no significant loss of AVP from the perfusate after treatment.

Coronary Flow

The coronary flow values for each group measured during the course of the experiments are shown in Figure 1. AVP treatment during normoxia (group 1, prehypoxia) resulted in a significant reduction of coronary flow to 61.6±2.6% of the initial value. Coronary flow in the control hearts did not change during this interval.

After the introduction of the hypoxic gas mixture (Figure 1, hypoxia 1), flow in the AVP-constricted coronary arteries increased considerably, returning coronary flow to the initial level. At this point, however, the coronary flow values were significantly higher in the hearts treated with hypoxia alone (group 3), in which a significant elevation of coronary flow over initial (+8.3±1.5%) was observed.

AVP treatment during the hypoxia period (group 2, hypoxia 2) also resulted in a significant reduction of coronary flow. However, coronary flow did not go below the initial value, and at the hypoxia 2 measurement point, the coronary flow values for both groups of AVP-treated hearts (groups 1 and 2) were the same.

When hypoxia was discontinued, significant reductions of coronary flow were observed in both AVP-treated groups of hearts (groups 1 and 2, posthypoxia 1). Coronary flow in the hearts that had been treated with hypoxia alone (group 3) remained somewhat higher than the flow in the normoxia controls (group 4) at this point.

Administration of the AVP antagonist to the four groups resulted in significant increases in coronary flow (i.e., coronary vasodilation) in the AVP-treated hearts. At the final (i.e., posthypoxia 2) measurement point, the coronary flow values of the four groups were similar; however, compared with the normoxia control hearts (group 4), the coronary flow values of the three groups of hypoxia-treated hearts (groups 1–3) were slightly, but significantly, lower at this point.

Coronary Venous Po2, MVo2, Stroke Work, and Cardiac Efficiency

The AVP treatment during normoxia (group 1) resulted in significant reductions of coronary venous Po2, MVo2, and stroke work (Figure 2, panels A–C, prehypoxia). Cardiac efficiency significantly increased with AVP treatment (Figure 2D, prehypoxia).

Hypoxia treatment also resulted in reductions of venous Po2 and MVo2 that were similar to those observed after AVP (Figure 2, panels A and B, hypoxia 1). However, stroke work was more affected by hypoxia than by AVP (Figure 2C), and unlike the response to AVP, cardiac efficiency was significantly depressed by hypoxia (Figure 2D).

AVP treatment during hypoxia (group 2, hypoxia 2) had little effect on venous Po2, MVo2, stroke work, or efficiency. As was also observed in the other AVP-treated group (group 1) during hypoxia, the effects of hypoxia predominated; there were no significant differences among the three hypoxia-treated

TABLE 2.  Per fusate Vasopressin Levels After Treatment

<table>
<thead>
<tr>
<th></th>
<th>Prehypoxia (pg/ml)</th>
<th>Hypoxia 2 (pg/ml)</th>
<th>Posthypoxia 1 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>777±67</td>
<td>821±36</td>
<td>791±72</td>
</tr>
<tr>
<td>Group 2</td>
<td>939±59</td>
<td>905±50</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM. Group 1, arginine vasopressin during normoxia; group 2, arginine vasopressin during hypoxia.
groups during the hypoxia period (hypoxia 1 and hypoxia 2).

On return to normoxia, the AVP-treated groups had values similar to those observed with AVP treatment before hypoxia (i.e., decreased venous PO₂ and MVO₂ and increased efficiency). In contrast, the venous PO₂ and MVO₂ values for the hearts treated with hypoxia alone (group 3) appeared to rebound, being higher than the normoxia control values (group 4) at this point (posthypoxia 1), while efficiency returned toward the control level.

Addition of the AVP antagonist reversed the effects attributed to AVP. There were no significant differences among the four groups for venous PO₂, MVO₂, stroke work, and efficiency values at the final (i.e., posthypoxia 2) measurement point.

Myocardial Function

Indexes of myocardial contractile function during the course of the experiments are shown in Figure 3. The responses of the various groups were similar to those described above for stroke work. Significant decreases in contractile function occurred with both AVP and hypoxia treatments, although the decrease in function after AVP alone (group 1, prehypoxia) was not as large as that observed after hypoxia alone (group 3, hypoxia 1). AVP treatment during hypoxia did not further affect contractile function (group 2, hypoxia 2). However, after the discontinuation of hypoxia, a small but significant depression of function was still apparent in both AVP-treated groups (posthypoxia 1). Administration of the AVP antagonist abolished the AVP-mediated effects on contractile function, and the four groups were indistinguishable at the final (i.e., posthypoxia 2) measurement point. Similar results were obtained for the −dP/dtₘₚₗ values (data not shown). LVEDP was not significantly affected by AVP but was significantly increased (+2–3 mm Hg) by hypoxia treatment. The LVEDP returned to initial values (3–5 mm Hg) when hypoxia was discontinued; LVEDP was not affected by the AVP antagonist.

The cardiac output and aortic output data are shown in Figure 4. AVP treatment during normoxia (group 1, prehypoxia) produced a slight, but significant, effect on cardiac output (Figure 4A). This appeared to largely reflect the decrease in coronary flow caused by AVP because there was no significant effect on aortic output (Figure 4B). Hypoxia treatment resulted in significant decreases in both aortic output and cardiac output (hypoxia 1). There were no significant effects on either aortic output or cardiac output resulting from AVP treatment during hypoxia (group 2, hypoxia 2). On return to normoxia, the AVP effect on cardiac output was again evident (groups 1 and 2, posthypoxia 1) and was reversed after administration of the AVP antagonist (posthypoxia 2).

Cardiac Lactate Production

The production of lactate during the course of the experiments is shown in Figure 5; the rate of lactate release calculated from these measurements is shown in Figure 6. AVP treatment alone resulted in a significant increase in the rate of lactate release (group 1, prehypoxia). However, hypoxia was accompanied by a substantially larger increase in lactate production in the three hypoxia-treated groups (hypoxia 1). On return to normoxia, perfusate lactate concentrations for the groups exposed to hypoxia declined (Figure 5, posthypoxia 1 and 2), reflecting the lactate uptake that occurred during this period (Figure 6).

Response to AVP During Normoxia Versus Hypoxia

A direct comparison of the cardiac effects of AVP treatment during normoxia and hypoxia (and values for the respective control groups) is shown in Figure 7. AVP treatment resulted in significant decreases in coronary flow and MVO₂ and increases in efficiency during both normoxia and hypoxia. However, these effects of AVP were significantly attenuated in the hypoxic hearts. In addition, indexes of contractile function (stroke work and dP/dtₘₚₗ) were significantly depressed by AVP treatment during normoxia only, indicating that these effects were also significantly attenuated during hypoxia.

Response to AVP Versus Hypoxia

The cardiac effects of AVP alone versus those of hypoxia alone are shown in Figure 8. Although the two treatments had differing effects on coronary flow (i.e., decreased by AVP and increased by hypoxia), both treatments had similar effects on
A. Venous $pO_2$

B. $\text{MV}O_2$

C. Stroke Work

D. Efficiency

Figure 2. Plots showing responses of each treatment group. Panel A: Venous $PO_2$. Panel B: $\text{MV}O_2$, myocardial oxygen consumption. Panel C: Stroke work. Panel D: Efficiency. AVP, arginine vasopressin; $\cdots \cdots$, AVP during normoxia (group 1); $\cdots$, AVP during hypoxia (group 2); $\cdots - \cdot - \cdot - \cdot$, hypoxia alone (group 3); $\cdots - \cdot - - -$, normoxia control (group 4). *Significantly different from control (group 4). †Significantly different from hypoxia alone (group 3). ‡Significant difference among groups by analysis of variance, no specific differences by Tukey's test. See legend to Figure 1 for other details.
myocardial O₂ supply, MVO₂, and O₂ supply/consumption ratios. Despite these similarities, hypoxia was associated with significantly more depression of cardiac contractile function than AVP, as evidenced by greater effects on stroke work, dP/dt max, and aortic output. In addition, AVP treatment significantly increased cardiac efficiency, whereas hypoxia produced a significant decrease. Additionally, the rate of lactate release was substantially higher during hypoxia (2.07±0.08 µmol/min) than during AVP treatment (0.76±0.05 µmol/min, p<0.05).
**A. Cardiac Output**

![Cardiac Output Graph](image1)

**B. Aortic Output**

![Aortic Output Graph](image2)

**Discussion**

The effects of AVP on the heart and coronary vasculature observed in this study agree with previously reported data. AVP administration during normoxia produced coronary constriction accompanied by myocardial depression and increased lactate release. The decrease in coronary flow in the absence of changes in the hemodynamic determinants of coronary perfusion as well as the coronary venous O₂ desaturation during AVP treatment are consistent with a direct effect of AVP on the coronary vessels. These effects are not consistent with an indirect effect, due to AVP-mediated decreases in myocardial oxygen demand or autoregulatory increases in coronary resistance.

The depressed contractile function and increased lactate release appeared to indicate that the AVP treatment compromised myocardial oxygen supply to the extent that myocardial ischemia was produced. However, the AVP-constricted coronary vessels dilated considerably in response to hypoxia and appeared to retain most of their metabolic vasodilatory reserve. This observation, as well as the diminished vascular response to AVP observed in the hypoxia-treated hearts, indicates that the coronary constricting effect of AVP was
attenuated during hypoxia. In addition, in contrast to the effect of AVP during normoxia, AVP treatment during hypoxia was not accompanied by significant myocardial depression.

Our findings appear to conflict with those of Pantely et al., who reported significant AVP-mediated coronary constriction at very low coronary perfusion pressures when the metabolic stimulus to vasodilate should be maximal. However, the brief period of coronary hypotension used in that study (10–15 seconds) may not have been sufficient to allow complete autoregulatory vasodilation. Additionally, the coronary pressure-flow data from that study indicate that the effect of AVP on coronary flow was attenuated as the coronary perfusion pressure was decreased, a result consistent with our finding that AVP-induced coronary constriction was attenuated during hypoxia. Similarly, other investigators have reported that AVP-constricted coronary vessels autoregulate normally in response to changes in perfusion pressure despite ischemic conditions. In this latter study, coronary flow was unaffected by AVP when perfusion pressure was reduced and 1–3 minutes was allowed for autoregulatory vasodilation. Thus, our findings are consistent with previous reports and indicate that autoregulatory factors attenuate the vasoconstricting effect of AVP. These findings suggest that the potentially deleterious effects of AVP on coronary flow and myocardial function would be attenuated or eliminated when oxygen supply to the heart was already compromised (i.e., during hypotension or hypoxia).

While both the AVP and hypoxia treatments produced identical reductions in myocardial oxygen supply and oxygen consumption, AVP had a significantly smaller effect on myocardial function than did hypoxia (Figure 8). In contrast, an earlier study indicated that cardiac function was depressed by a comparable amount when myocardial oxygen supply was reduced to the same extent by decreasing either coronary flow or oxygen content of the coronary perfusate. In addition, other studies indicate that ischemia (i.e., reduced coronary flow) is generally accompanied by greater myocardial dysfunction than that which accompanies hypoxia. Thus, considering the degree of myocardial depression associated with hypoxia in our study, the amount of cardiac depression associated with AVP-mediated ischemia appeared to be less than expected.

The better maintenance of cardiac function during AVP treatment compared with that during hypoxia treatment appeared to be related to the more efficient use of the available oxygen supply by the AVP-treated hearts. In contrast to the marked decrease in efficiency observed during hypoxia treatment, a significant increase in cardiac efficiency was
observed in the AVP-treated hearts. Using a protocol similar to ours, other investigators have reported that hypoxia decreased cardiac efficiency.\textsuperscript{34} Decreased efficiency during ischemia has also been observed,\textsuperscript{35} an effect attributed to increased oxygen demand for noncontractile processes or uncoupling of oxidative phosphorylation.\textsuperscript{36,37} Thus, the effect of AVP treatment versus hypoxia treatment on efficiency does not appear to represent a difference between ischemia and hypoxia per se but, rather, suggests an effect of AVP that prevents the expected decrease in both efficiency and cardiac function.

We also observed less lactate production during AVP treatment compared with that observed during hypoxia. Although this difference could be attributed to greater tissue accumulation of lactate and inhibition of glycolysis during ischemia,\textsuperscript{11,31,38,39} glycolytic inhibition also results in greater depression of contractile function during ischemia compared with that observed during hypoxia.\textsuperscript{11,31} Because function was less depressed during AVP treatment, inhibition of glycolysis may not be the reason for the lower lactate release during AVP treatment. Rather, as a result of more efficient use of oxygen, the AVP-treated hearts may have been less dependent on glycolysis as an anaerobic source of energy.

Previously, we proposed that the AVP-induced increase in cardiac efficiency may have resulted from a metabolic “shift” toward anaerobically derived ATP, as evidenced by the production of lactate.\textsuperscript{1} Although this could explain the increased efficiency occurring with AVP treatment, it is not consistent with the effect of hypoxia that produced a decrease in efficiency despite greater lactate release. Indeed, if anaerobic energy production were also taken into account in calculating cardiac efficiency, the negative effect of hypoxia on efficiency, as well as the difference between the hypoxia and AVP treatments, would be even larger.

Administration of inotropic agents to isolated hearts is accompanied by increased efficiency\textsuperscript{25} similar in magnitude to that observed during AVP treatment. Although a similar mechanism could explain the increase in efficiency during AVP treatment as well as the higher than expected contractile function in the AVP-treated hearts, a positive inotropic effect would appear difficult to reconcile with several reports suggesting a direct negative inotropic effect of AVP.\textsuperscript{6-10} However, a direct depressant effect of AVP has not been demonstrated in the absence of direct coronary constriction,\textsuperscript{5,7,10} unless very large AVP doses were used.\textsuperscript{8,9} In experiments in which coronary flow was maintained during AVP treatment, evidence of myocardial depression was absent.\textsuperscript{3} The fact that AVP treatment during hypoxia (in which the coronary constricting effect was largely eliminated) had no significant effect on contractile function in our experiments also appears to argue against a direct myocardial depressant effect of AVP at physiologically relevant concentrations.

In the absence of a direct myocardial effect, improvement in the distribution of coronary flow may represent another potential mechanism to explain the positive effect of AVP (and other agents) on cardiac efficiency. The finding that AVP treatment resulted in increased efficiency and well-maintained global cardiac function despite the large decrease in oxygen supply suggests that AVP selectively constricted vascular beds that were unimportant for efficient utilization of oxygen or maintenance of cardiac function. The observed modulation of AVP’s coronary vascular effect during hypoxia could provide an explanation for this selectivity. In regions of the heart with relatively low O\textsubscript{2} supply/demand ratios, the metabolic stimulus to vasodilate would be expected to be intense, and AVP would thus be expected to have little effect on flow. Conversely, in regions where the O\textsubscript{2} supply/demand ratio was relatively high and the stimulus to vasodilate was less intense, AVP would be expected to have a more marked constricting effect. Therefore, the overall effect of AVP would be tighter matching of regional intracardiac distribution of blood flow according to tissue demands, while keeping total coronary flow to a minimum. We propose that this more efficient distribution of flow could account for the more efficient utilization of oxygen as well as a relatively small effect of AVP on cardiac function. Such an effect could have significant physiological importance in conditions such as hemorrhage, hypotension, and

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Cardiac responses to arginine vasopressin (AVP) alone (●) versus hypoxia alone (■). MV\textsubscript{O}\textsubscript{2}, myocardial oxygen consumption. *Significantly different from AVP.}
\end{figure}
hypoxia when AVP levels are high enough to produce coronary constriction. Although cardiac α-adrenergic blockade during exercise was associated with higher overall coronary flow and myocardial function, the transmural distribution of flow was more uniform and flow to the endocardium was better maintained with the α-adrenergic response intact. Thus, α-adrenergic-mediated coronary constriction was proposed to be physiologically important in maintaining coronary flow to the more oxygen-deprived endocardium during exercise.

As we have proposed for AVP, modulation of norepinephrine-mediated coronary constriction by metabolic vasodilatory factors could account for the more uniform distribution of flow between the relatively oxygen-deprived endocardium and the more generously perfused epicardium during exercise. Furthermore, the systemic (i.e., noncardiac) vasoconstricting effects of both AVP and norepinephrine are also considered, the physiological significance of the coronary vascular effect may be more apparent. By producing direct vascular constriction in the systemic as well as the coronary circulation, hypotension due to intense metabolic vasodilation would be prevented, while attenuation of the vasoconstriction by metabolic vasodilatory factors would allow preservation of perfusion to vital tissues such as the endocardium. Therefore, the coronary constricting effect of AVP and norepinephrine may be part of an important physiological response that serves to maintain adequate perfusion and function of vital tissues when the ability of the cardiovascular system to meet tissue oxygen demands is threatened. This would be accomplished not by indiscriminate vasoconstriction but by integrating the effects of metabolic vasodilatory factors such that the available oxygen is most efficiently used.

Our data indicate that AVP-mediated ischemia differs considerably from ischemia associated with a proximal coronary obstructing lesion. In contrast to the effects of AVP, a decrease in efficiency and a more marked effect on global function are observed in this latter situation. In addition, coronary stenosis would preferentially affect flow to regions with low O₂ supply/demand ratios and little vasodilatory reserve (i.e., endocardium), while flow to areas with higher O₂ supply/demand ratios (i.e., epicardium) could be maintained by further vasodilation. In fact, vasodilation in the epicardium could further reduce the postobstruction perfusion pressure and thus result in a further reduction of flow (i.e., “coronary steal”) to the more oxygen-deprived endocardium. As Feig proposed for norepinephrine-mediated coronary constriction, AVP might also prevent coronary steal by selectively constricting only those beds supplying regions with high O₂ supply/demand ratios while having little effect in more oxygen-deprived regions. However, despite this potential benefit of AVP (or norepinephrine) in patients with coronary disease, AVP is clearly capable of precipitating ischemia in such patients, and as already discussed, myocardial infarction has been well-documented after AVP administration. Perhaps patients with coronary disease have exaggerated responses to AVP, as may also be true for other potent coronary constricting agents. Diffuse endothelial damage associated with the arteriosclerotic process may be the mechanism for such increased vascular responsiveness, and as has been shown for both AVP and other coronary constrictors, the endothelium plays an important role in modulating the vascular response. Thus, although our study suggests that AVP would have little effect on coronary flow when myocardial oxygen supply is decreased in “normal” hearts, conclusions cannot be drawn regarding the effect of AVP on coronary flow in patients with coronary vascular disease.

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