Integrated Cardiac, Renal, and Endocrine Actions of Endothelin

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Abstract

Endothelin, a newly discovered endothelial-derived peptide, has been demonstrated in vitro to have potent vasoconstrictive properties and has been speculated to play a role in vivo in arterial pressure-volume homeostasis. The present studies in anesthetized dogs were designed to determine the action of endothelin on cardiovascular-renal and endocrine function in vivo as in acute arterial pressure-volume regulation. Intravenous infusion of endothelin (50 ng/kg per min) increases arterial pressure by increasing peripheral vascular resistance but in association with an increase in coronary vascular resistance and decreases in cardiac output. Renal blood flow and glomerular filtration rate were markedly reduced in association with a sustained reduction in sodium excretion and an increase in plasma renin activity. Atrial natriuretic factor, vasopressin, and aldosterone were also elevated. These results indicate that endothelin is a potent constrictor that elevates systemic blood pressure in association with marked decreases in cardiovascular and renal function. This peptide may function as a counterregulatory hormone to the effects of endothelial-derived vasodilator agent(s).

Introduction

A new peptide of vascular endothelial origin has been recently isolated from the cultured supernatant of porcine aorta (1). This 21-aa amino acid residue peptide, endothelin, has been demonstrated to be a potent constrictor of vascular smooth muscle in vitro, which may be dependent upon extracellular calcium (1). In addition to the production of an endothelial-derived vasoconstriction, the vascular endothelium is well recognized to produce relaxation of vascular smooth muscle through the release of short-lived endothelium-derived relaxing factor(s) (EDRF) (2). The production by the endothelium

1. Abbreviations used in this paper: Aldo, aldosterone; ANF, atrial natriuretic factor; CBF, coronary blood flow; CO, cardiac output; CVR, coronary vascular resistance; EDRF, endothelium-derived relaxing factor(s); FENa+, fractional excretion of sodium; (L)AP, left atrial pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PRA, plasma renin activity; PVR, peripheral vascular resistance; (R)AP, right atrial pressure; RBF, renal blood flow; RVR, renal vascular resistance; SVR, systemic vascular resistance; U\text{Na}^+, sodium excretion.

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MN) was advanced from the isolated right external jugular vein through the right cardiac chamber and positioned in a pulmonary artery. Right atrial, pulmonary artery, and pulmonary artery wedge pressures were measured. Cardiac output (CO) was determined in triplicate by the thermodilution technique with a cardiac output computer (model 9510-A, American Edwards Laboratories, Inc.).

**Experimental protocol.** After completion of surgical preparations and initiation of insulin and isotonic saline infusions at 1 ml/min the dogs were allowed to stabilize for 60 min without intervention. Subsequently, two consecutive 15-min baseline clearances were obtained. Each clearance, either baseline or subsequently with infusion of endothelin, consisted of a 15-min urine collection, measurement of hemodynamic parameters, and the withdrawal of 25 cm of arterial blood for hormone, electrolyte, and inulin determinations. Systemic intravenous infusion of endothelin (0.05 µg/kg per min; Peninsula Laboratories, Inc., Belmont, CA) was begun after the baseline clearances. The purity of this peptide is >95% based upon HPLC analysis. After a 15-min lead-in infusion of endothelin, the first of three consecutive 15-min clearances was begun. The total time of endothelin infusion was 60 min. After the last endothelin clearance period the infusion was discontinued and a 60-min washout period was observed. A final 15-min clearance (recovery) was then obtained to complete the experimental protocol.

**Analytical procedures.** GFR was measured by the clearance of inulin. Plasma and urine inulin concentrations were measured by the anthrone method (4). Plasma and urinary sodium concentrations were determined using ion-selective electrodes (system E2A, Beckman Instruments, Inc., Palo Alto, CA). PRA, aldosterone, and arginine vasopressin (AVP) levels were measured by RIA as previously reported (5). Extracted arterial plasma levels of atrial natriuretic factor (ANF) were measured by an RIA procedure previously described (6).

Data from the two baseline clearances were combined and the mean values calculated. Data from the endothelin infusion periods and the recovery periods are expressed separately with all data expressed as mean±SEM. Statistical analysis of data was completed by t tests for paired and unpaired observations. Statistical significance was accepted for P < 0.05.

**Results**

Table I summarizes the systemic, cardiac, and pulmonary hemodynamic data during baseline, intravenous infusion of endothelin, and 1-h postinfusion periods for six normal dogs. Mean arterial pressure (MAP) increased significantly above baseline with endothelin infusion, achieving the maximum increase in pressure after 45 min of infusion (99±7-134±6 mmHg, P < 0.05). Pressure then declined despite continued endothelin infusion and a further increase in systemic vascular resistance (SVR). This was also associated with a significant decrease in CO. At 1 h postinfusion MAP returned to baseline, but this was accomplished with persistent decreases in CO and increases in SVR.

Pulmonary artery wedge pressure as an index of left atrial pressure [(L)AP] was elevated with endothelin infusion. The most significant rise above baseline occurred after 45 min of continuous infusion (2.5±0.4-9.1±3.4 mmHg, P < 0.05). Wedge pressure decreased toward baseline at 1 h postinfusion, but nevertheless remained significantly elevated. In contrast, right atrial pressure [(R)AP] was not changed from baseline (3.1±1.3 mmHg) with endothelin infusion. Left circumflex coronary artery flow also tended to decrease with endothelin but the decrease was not statistically significant. Coronary vascular resistance (CVR), however, was significantly elevated in the second and third clearance periods of endothelin infusion but then returned to baseline in the recovery period. Mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR) were unchanged with endothelin infusion or with recovery.

Table II summarizes the renal hemodynamic and excretory function data during baseline, endothelin infusion, and 1-h postinfusion periods. With endothelin infusion glomerular filtration rate and renal blood flow (RBF) were significantly reduced beginning from the first clearance period of endothelin infusion. RBF was dramatically decreased by endothelin to ~23% of baseline flow. Renal vascular resistance (RVR) showed a correspondingly significant increase with endothelin infusion. At 1 h postinfusion neither blood flow nor RVR had recovered to baseline, with RBF remaining at ~65% of baseline. GFR, in contrast, was significantly elevated above baseline during recovery (38.5±3.6-47.7±2.1 ml/min, P < 0.05) in contrast to RBF, which remained depressed. Urine flow and sodium excretion [U_{Na+}V] were immediately reduced in association with the decreased renal hemodynamics. While urine flow was restored to baseline at 1 h postinfusion, U_{Na+}V remained depressed compared with baseline (47.6±14.3-12.6±3.6 meq/min). Fractional sodium excretion (F_{Na+}) was not significantly decreased from baseline during endothelin infusion, but did decline significantly despite termination of endothelin infusion. At 1 h postinfusion F_{Na+} was significantly depressed (0.95±0.71-0.18±0.05%, P < 0.05). F_{Na+} was the only parameter monitored, hemodynamic or renal function, that did not show some recovery toward baseline.
Table II. Renal Hemodynamic and Excretory Effects of Endothelin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Endothelin (50 ng/kg per min)</th>
<th>Recovery (1 h postinfusion)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>38.5±3.64</td>
<td>4.26±1.31*</td>
<td>1.43±0.39*</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>267±33</td>
<td>136±21*</td>
<td>87±14*</td>
</tr>
<tr>
<td>RVR (mmHg·ml⁻¹·min⁻¹)</td>
<td>0.398±0.049</td>
<td>1.043±0.172*</td>
<td>1.702±0.212*</td>
</tr>
<tr>
<td>Urine volume (ml/min)</td>
<td>0.27±0.082</td>
<td>0.03±0.009*</td>
<td>0.012±0.001*</td>
</tr>
<tr>
<td>UNa⁺V (µg/min)</td>
<td>47.6±14.3</td>
<td>4.56±0.48*</td>
<td>1.23±0.26*</td>
</tr>
<tr>
<td>FENa⁺ (%)</td>
<td>0.95±0.31</td>
<td>0.88±0.17</td>
<td>0.66±0.14</td>
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</tbody>
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*±SEM, n = 6.  *P < 0.05.  † sodium detected; insufficient urine volume collected for determination.

Table III. Endocrine Effects of Endothelin

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Endothelin (50 ng/kg per min)</th>
<th>Recovery (1 h postinfusion)</th>
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<tbody>
<tr>
<td></td>
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<td>1</td>
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<tr>
<td>ANF (pg/ml)</td>
<td>39.4±5.90</td>
<td>64.9±12.81*</td>
<td>116.8±30.8*</td>
</tr>
<tr>
<td>PRA (ng/ml)</td>
<td>3.72±1.02</td>
<td>7.29±2.28*</td>
<td>7.08±2.49</td>
</tr>
<tr>
<td>Aldo (ng/ml)</td>
<td>11.6±3.34</td>
<td>23.5±6.16*</td>
<td>28.9±8.11*</td>
</tr>
<tr>
<td>AVP (pg/ml)</td>
<td>8.45±2.76</td>
<td>5.05±2.60</td>
<td>9.43±2.97</td>
</tr>
</tbody>
</table>

*±SEM, n = 6.  *P < 0.05.
baseline with cessation of endothelin infusion. This may reflect a waning effect of endothelin preferentially on afferent arteriolar resistance and/or the effect of a sustained elevation in ANF which has afferent arteriole vasodilatory properties and/or actions upon glomerular function to increase $K_f$, the ultrafiltration coefficient.

The endocrine data support the hypothesis that endothelin stimulates renin activity in vivo. This finding, in view of the recent report of Vidal et al. that EDRF inhibits renin production in canine renal cortical slices, suggests that endothelin may function physiologically to antagonize the effects of EDRF (3). Alternatively, endothelin may serve to activate renin by decreasing delivery of sodium to the macula densa, which is consistent with its action on GFR and proximal tubule reabsorption as GFR decreased in association with an increase in proximal tubule reabsorption. An interaction of renin with ANF is also suggested by these data as PRA was maximally stimulated in the initial period of endothelin infusion and thereafter declined as ANF levels progressively increased. This is based on the recognized action of ANF to inhibit renin activation. The elevated but plateaued levels of PRA may, therefore, reflect the influence of the progressive elevation of ANF. The progressive rise in ANF with endothelin infusion corresponds to the progressive rise in (L)AP also observed with endothelin infusion. This supports previous reports of the mechanism of ANF release through elevation in atrial pressure. The sustained elevation in ANF at 1 h postinfusion is also reflected in the sustained increase in (L)AP. In association with activation of renin, plasma aldol was also increased.

AVP was unchanged during the initial periods of endothelin infusion, but subsequently increased. This occurred despite elevated ANF as well as increased (L)AP, which are both inhibitors of vasopressin release.

In summary, these data demonstrate that endothelin is a potent vasoconstrictive peptide in vivo with a preferential effect on the renal circulation in association with a significant effect upon the peripheral circulation to increase overall systemic resistance. A sustained antinatriuretic effect was also produced by endothelin despite significant elevations in ANF. PRA is also stimulated by endothelin as is AVP. The potential for endothelin to contribute to pathophysiologic states such as hypertension, vasospasm, and congestive heart failure remains to be investigated as does the interaction of endothelin with other endothelium-derived vasoactive agents such as EDRF.

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**References**


