Estrogen restores role of basal nitric oxide in control of vascular tone in rats with chronic heart failure

ALI AKBAR NEKOOEIAN AND CATHERINE C. Y. PANG
Department of Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z3


Estrogen restores role of basal nitric oxide in control of vascular tone in rats with chronic heart failure. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H2094–H2099, 1998.—This study examined the cardiovascular effects of 17β-estradiol in ovariectomized rats with heart failure. Two groups (50–60 days old) were implanted with 60-day-release pellets containing 17β-estradiol (25 µg/day) or vehicle at 7 days before ligation of the left coronary artery. Another group was sham operated and given vehicle pellets. After 7 wk, they were studied under pentobarbital anesthesia. Relative to sham-operated rats, ligated rats had reduced mean arterial pressure (MAP, 24 ± 6 mmHg), cardiac output (27 ± 4 ml/min), left ventricular (LV) end-systolic pressure (29 ± 8 mmHg), depressor responses to ACh (6 ± 4 mmHg at 7.2 µg/kg) and sodium nitroprusside (SNP, 22 ± 6 mmHg at 9 µg/kg), and pressor responses to Nω-nitro-L-arginine methyl ester (L-NAME, 14 ± 6 mmHg at 8 mg/kg) and increased LV end-diastolic pressure (LVEDP, 10.3 ± 0.8 mmHg) but no change in total peripheral resistance (TPR). Treatment of ligated rats with 17β-estradiol reduced TPR (0.19 ± 0.06 mmHg·min·ml⁻¹), LVEDP (3.6 ± 1 mmHg), and responses to ACh (16 ± 4 mmHg) and augmented responses to L-NAME (14 ± 3 mmHg) but did not alter other variables. Therefore, 17β-estradiol reduces preload and afterload and restores the vasodilator role of basal nitric oxide in ovariectomized rats with chronic heart failure.

17β-estradiol; Nω-nitro-L-arginine methyl ester; cardiac output; acetylcholine; left ventricular end-diastolic pressure

EPIDEMIOLOGIC STUDIES show that estrogen replacement therapy after menopause reduces the morbidity and mortality of coronary artery diseases (33). The mechanism by which estrogen reduces the risk of heart diseases is unclear because estrogen has multiple cardiovascular actions. Estrogen reduces the plasma concentration of low-density lipoproteins and increases that of high-density lipoproteins (for review, see Ref. 4). It has been suggested that many of the cardioprotective effects of estrogens are caused by mechanisms distinct from alterations in lipid metabolism (1). Estrogens have prominent vascular actions in vitro and in vivo. In vitro studies show that 17β-estradiol relaxes vascular smooth muscle via endothelium-dependent (23) as well as endothelium-independent (25) mechanisms. It also potentiates relaxation of isolated blood vessels elicited by endothelium-dependent (6) as well as endothelium-independent (5) agents. Moreover, estradiol has been shown to potentiate (38) as well as attenuate (23) contractions in response to α-adrenoceptor agonists.

17β-Estradiol, infused close arterially, caused vasodilatation of epicardial and resistance coronary arteries of dogs (35) and potentiated endothelium-dependent as well as -independent vasodilatation of the human forearm (16). Intravenous injection of ethinyl estradiol into postmenopausal women dilated epicardial and resistance coronary arteries (29). Intravenous infusion of 17β-estradiol into the coronary artery of postmenopausal female patients (8) and injection of ethinyl estradiol into atherosclerotic monkeys (42) converted ACh-induced constriction to dilatation in the epicardial coronary artery. Administered chronically, 17β-estradiol reduced mean arterial pressure (MAP) (37) as well as total peripheral resistance (TPR) and increased cardiac output (CO) (24) in ovariectomized sheep. Chronic treatment of monkeys with 17β-estradiol did not alter MAP but increased CO and reduced TPR (45). It is therefore evident that estrogens have direct as well as indirect vasodilator actions in healthy animals.

Estrogen replacement is a common practice in western culture. There are epidemiologic indications that estrogen replacement after natural menopause or surgical ovariectomy reduces the risk of coronary artery disease. The cardiovascular effects of estrogens in animals with heart failure are not known. This study investigated whether the replacement of estrogen in ovariectomized rats with chronic heart failure inhibited the declines in cardiovascular function associated with chronic heart failure, i.e., the declines in CO as well as myocardial contractility and the reductions in MAP responses to vasodepressor and vasopressor drugs (12, 20, 21, 34, 39). The drugs examined included the endothelium-dependent vasodilator and vasoconstrictor ACh and Nω-nitro-L-arginine methyl ester (L-NAME, nitric oxide synthase inhibitor), respectively, as well as the endothelium-independent vasodilator and vasoconstrictor, sodium nitroprusside (SNP) and norepinephrine (NE) (mixed α- and β-adrenoceptor agonist), respectively.

METHODS

Implantation of pellets and ovariectomy. Age-matched (50–60 days) female Sprague-Dawley rats were anesthetized with halothane and implanted subcutaneously at the back of the neck with 60-day-release pellets (Innovative Research of America, Sarasota, FL) containing vehicle or 17β-estradiol (1.5 mg). Ovariectomy was performed through a small midline incision on the skin of the lower back. The skin incision was moved over to the right as well as the left flank areas to allow the resection of both ovaries. After application of bupivacaine (local anesthetic) and Cicatrin (bacitracin-neomycin powder) to the wound, the skin incision was closed. Another group of age-matched intact rats not implanted with pellets was used to determine control serum estradiol concentration and uterine weight (see Measurement of serum 17β-estradiol).
estradiol). All animals were kept on a 12:12-h light-dark cycle with standard rat chow and water ad libitum.

Coronary artery ligation. One week later, under halothane anesthesia, vehicle-treated rats were subjected to sham operation (V-S) or ligation of the left main coronary artery (V-CL). A third group pretreated with 17β-estradiol was given coronary artery ligation (E-CL). Briefly, a left thoracotomy was performed at the level of the fourth intercostal space to expose the heart. The left main coronary artery was ligated at 2–4 mm from its origin using 6–0 prolene. In the sham-operated rats, the suture was passed through but the artery was not ligated. Afterwards, bupivacaine and Cicatrin were applied and the incisions were closed in layers. The rats were recovered from anesthesia and housed under the conditions described in Implantation of pellets and ovariectomy. The intact rats to be used for the measurement of serum estradiol concentration were not subjected to sham operation or coronary artery ligation.

Acute surgical preparation. Seven weeks later, the rats were anesthetized with pentobarbital sodium (65 mg/kg ip). Catheters (PE-50) were inserted into both iliac arteries, for measurement of MAP and withdrawal of a reference blood sample (0.35 ml) for CO determinations (see Calculations and statistical analysis), and the left iliac vein, for administration of drugs or anesthetic as needed. Another catheter was inserted via the right carotid artery into the left ventricle (LV) for the measurement of LV end-diastolic pressure (LVEDP) and end-systolic pressure (LVEP). Pressures and injection of radioactively labeled microspheres. All catheters were filled with heparinized normal saline (25 IU/ml). The body temperature was maintained at 37°C via a rectal thermometer and a heating pad connected to a Thermistemp Instrument Controller (model 71, Yellow Spring Instruments). MAP, LVEDP, and LVEP were recorded with a pressure transducer (PD 23B Gould Statham) connected to a Grass polygraph (model PR5T7BB). The rate of rise of LV pressure (dP/dt) was quantified using an electronic differentiator (Grass, model 7P20C). Heart rate (HR) was counted from the upstroke of the arterial pulse pressure. CO was measured by the injection of 125I-labeled microspheres (25,000–30,000 spheres, 15-µm diameter, New England Nuclear) and the removal of a reference blood sample (4). A Searle 1185 series automatic gamma counter was used for the counting of radioactivity. The rats were used 1 h after the completion of surgery.

Experimental protocol. A blood sample (0.6 ml) was taken from each of the three groups (n = 6 each) of ovariectomized rats (V-S, V-CL, and E-CL) as well as the group (n = 6) of intact rats for measurements of serum concentrations of 17β-estradiol. After baseline measurements of MAP, CO, HR, LVEDP and LVEP were obtained in the three groups of ovariectomized rats, MAP dose-response curves to single intravenous bolus injections of NE (0.1, 0.3, 0.9, and 1.8 µg/kg at dose intervals of 1–5 min to allow complete recovery of responses), ACh (0.8, 2.8, and 7.2 µg/kg at dose intervals of 1–5 min to allow complete recovery), and SNP (1, 3, and 9 µg/kg at dose intervals of 1–5 min to allow complete recovery) and a single cumulative intravenous bolus of L-NAME (2, 4 and 8 mg/kg at dose intervals of 10 min with no recovery of responses) were carried out. At the end of the experiments the rats were killed by an overdose of pentobarbital, the uteri were cleaned of surrounding tissues and weighed, the hearts were excised, and the surface areas of myocardial infarct were quantified.

Assessment of surface area of infarct. The modified method of Chien and colleagues (7) was used to quantify the area of infarct. Briefly, after the atria was cut away, the ventricle was cleaned of blood and a saline-filled balloon was inserted into the LV. The balloon was inflated and sealed, and the heart was placed in 100% Formalin. Fixation in Formalin helps to preserve the size of the heart and reduces either over- or underestimation of the size of tissue with infarct relative to the area without infarct. After 24 h, in a blinded fashion, the right ventricle was trimmed away. An incision was made in the LV so that the tissue could be flattened and traced. The circumferences of the LV and infarct were outlined on a plastic sheet for both the endocardial and epicardial surfaces over a source of light, which sharpens the demarcation of the areas with or without infarct. The endocardial and epicardial surface areas were averaged. The area of infarct was calculated as a percentage of LV surface area, estimated by the proportional weights of the areas marked on the plastic sheet. Measurement of serum 17β-estradiol. The blood samples were allowed to clot for >30 min, and this was followed by centrifugation at 10,000 rpm for 10 min to separate the serum samples, which were stored at −20°C. Serum concentrations of estradiol were measured using an 125I-labeled radioimmunoassay kit (ICN Biomedicals, Costa Mesa, CA). The intra-assay and interassay coefficients of variation are 4.7 and 9.1%, respectively, and the limit of detection of the assay is from 10 to 3,000 pg/ml. All samples, including the standard curve, were run in duplicate, and the average is reported.

Drugs. NE, ACh, L-NAME (Sigma Chemical, St. Louis, MO), and SNP (Fisher Scientific) were dissolved in normal saline (0.9% NaCl).

Calculations and statistical analysis. CO and TPR were calculated as follows

\[
\text{CO (ml/min)} = \frac{\text{rate of withdrawal of blood (ml/min) \times total injected cpm}}{\text{cpm in withdrawn blood}}
\]

where cpm is counts per minute.

Regression analyses of HR on MAP in response to various doses of SNP as well as L-NAME were carried out to estimate the baroreflex status of each of the three groups of rats. MAP dose-response curves were analyzed with single-factor repeated-measure ANOVA. Other data were analyzed by one-way ANOVA. All data were tested for homogeneity of variance before statistical analysis using Bartlett's homogeneity of variance test. Except for MAP responses to ACh and L-NAME and mortality, all data had homogeneity of variance. The ACh and L-NAME data were log transformed to render the variances homogeneous before statistical analysis. Where significant differences were obtained from ANOVA, the source of the difference was located by Duncan's multiple-range test, with P < 0.05 as the criterion for statistical significance. Significant difference in mortality was evaluated by a nonparametric test using a fourfold contingency table for unequal samples at P < 0.05. Hemodynamic and MAP responses to NE and SNP are reported as means ± SE, whereas MAP responses to ACh and L-NAME are reported as means ± confidence limit.

RESULTS

Serum concentration of 17β-estradiol in intact rats was 200 ± 48 pg/ml. Ovariectomy reduced serum estradiol to 107 ± 9 and 99 ± 10 pg/ml, respectively, in the V-S and V-CL groups. Implantation of pellets containing 17β-estradiol restored serum estradiol to
207 ± 19 pg/ml at 7 wk after ligation of the left main coronary artery.

Uterine weight of the intact rats was 0.41 ± 0.03 g. Uterine weight was reduced to 0.15 ± 0.01 and 0.14 ± 0.01 g, respectively, in the ovariectomized V-S and V-CL groups. Uterine weight (0.42 ± 0.03 g) was unchanged by ovariectomy in rats implanted with pellets containing 17β-estradiol.

The coronary-ligated groups, V-CL and E-CL, had similar surface areas of infarct (Table 1) and mortalities of 45 and 33%, respectively, at 7 wk postligation. There was no infarct area or mortality in the V-S group. The V-CL group had increased (+67%) wet lung weight, and this increase was abolished by pretreatment with 17β-estradiol. Ventricular weights were not statistically different among the three groups. Body weight was unaffected by coronary ligation, but it was lower (−29%) in the 17β-estradiol-treated group.

Relative to the V-S group, the V-CL group had significantly lower MAP, CO, LVEDP, and dP/dt; significantly higher LVEDP, nonsignificantly higher TPR, and no change in HR (Table 2). 17β-Estradiol reduced LVEDP and TPR but did not significantly alter other cardiovascular variables (Table 2).

Curve analysis shows that coronary ligation attenuated pressor responses to L-NAME and depressor responses to ACh and SNP but did not significantly alter pressor responses to NE (Figs. 1 and 2). 17β-Estradiol increased pressor responses to L-NAME and further reduced depressor responses to ACh but did not alter responses to SNP and NE.

The baroreflex activity in each of the three groups of rats, V-S, V-CL, and E-CL (estimated by ANOVA of the regression relationship of HR on MAP in response to SNP and L-NAME), was not statistically significant in any group.

**DISCUSSION**

Our results show that ovariectomized rats subjected to ligation of the left main coronary artery develop chronic heart failure characterized by decreased MAP, CO, LVEDP, and dp/dt and increased LVEDP and lung weight at 7 wk after the operation. These cardiovascular changes are consistent with those reported in rats with chronic heart failure elicited by ligation of the coronary artery (31). The mortality rate in vehicle-treated, ovariectomized rats subjected to coronary ligation was 45% at 7 wk postligation.

### Table 1. Left ventricular infarct area and ventricular, lung and body weights of V-S, V-CL, and E-CL rats

<table>
<thead>
<tr>
<th></th>
<th>V-S</th>
<th>V-CL</th>
<th>E-CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct area, %</td>
<td>33.7 ± 1.9</td>
<td>31.2 ± 1</td>
<td></td>
</tr>
<tr>
<td>Ventricular weight, g</td>
<td>0.94 ± 0.03</td>
<td>1.02 ± 0.06</td>
<td>0.97 ± 0.02</td>
</tr>
<tr>
<td>Lung weight, g</td>
<td>1.32 ± 0.07</td>
<td>2.20 ± 0.30*</td>
<td>1.38 ± 0.07†</td>
</tr>
<tr>
<td>Body weight, g</td>
<td>357 ± 14</td>
<td>336 ± 19</td>
<td>240 ± 7†</td>
</tr>
</tbody>
</table>

Values are means ± SE. V-S, vehicle treated, sham operated; V-CL, vehicle treated, coronary artery ligated; E-CL, 17β-estradiol treated, coronary artery ligated. *Significantly (P < 0.05) different from V-S rats; †significantly different from V-CL rats.

### Table 2. Baseline cardiovascular variables of V-S, V-CL, and E-CL rats

<table>
<thead>
<tr>
<th></th>
<th>V-S</th>
<th>V-CL</th>
<th>E-CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>104 ± 2</td>
<td>80 ± 5*</td>
<td>76 ± 3*</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>83 ± 3</td>
<td>56 ± 2*</td>
<td>61 ± 3*</td>
</tr>
<tr>
<td>TPR, mmHg·min·ml⁻¹</td>
<td>1.26 ± 0.06</td>
<td>1.42 ± 0.07</td>
<td>1.23 ± 0.02†</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>367 ± 7</td>
<td>340 ± 11</td>
<td>327 ± 7</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>-1.5 ± 0.8</td>
<td>8.8 ± 0.7*</td>
<td>5.3 ± 1.0†</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>123 ± 4</td>
<td>93 ± 5*</td>
<td>83 ± 1*</td>
</tr>
<tr>
<td>+dp/dt, mmHg/s</td>
<td>4,725 ± 85</td>
<td>3,208 ± 187*</td>
<td>2,900 ± 91*</td>
</tr>
</tbody>
</table>

Values (n = 6) are means ± SE of mean arterial pressure (MAP), cardiac output (CO), total peripheral resistance (TPR), heart rate (HR), left ventricular (LV) end-diastolic pressure (LVEDP), LV end-systolic pressure (LVESP), and rate of rise of LV pressure (+dp/dt). *Significantly (P < 0.05) different from V-S rats; †significantly different from V-CL rats.

Ovariectomy reduced serum 17β-estradiol in V-S and V-CL rats to approximately one-half that of age-matched intact rats (200 ± 48 pg/ml); the latter reading represents the mean serum concentration of 17β-estradiol and not that at a certain stage of the estrous cycle.
EFFECTS OF ESTROGEN IN CHRONIC HEART FAILURE.

Fig. 2. Effects of intravenous bolus of ACh (means ± confidence limit; A) and sodium nitroprusside (means ± SE; B) on MAP (mmHg) of V-S, V-CL, and E-CL groups (n = 6 each). Changes in MAP are from baselines immediately before individual injections. ACh data have been log transformed to render variances homogeneous before statistical analysis. *Significantly (P < 0.05) different from V-S; †Significantly different from V-CL.

cycle. The sustained-release pellets restored serum estradiol to a concentration comparable to that of intact rats. Because rats have their first estrous cycle at 37 days (3), the rats in the present study were ovariectomized at 13–23 days postestrus. Therefore, estrogen treatment represented a replacement therapy. Ovariectomy also reduced uterine weights by 65% in the V-S and V-CL groups. Replacement with 17β-estradiol (E-CL) abolished the fall in uterine weight in ovariectomized rats.

Ligated rats treated with estradiol (E-CL) also had lower body (−29%) and lung (−37%) weight relative to rats treated with vehicle (V-CL). Reduced body weight in response to 17β-estradiol has been reported (10). Reduced lung weight could be caused by reduced body weight as well as pulmonary congestion, as indicated by reduced LVEDP. 17β-Estradiol did not significantly alter mortality, area of infarct, or ventricular weight relative to the corresponding readings in the vehicle-treated group with coronary ligation. However, ischemia and reperfusion studies show that 17β-estradiol reduced the size of myocardial infarct (17, 26). The condition of the present study, using rats with permanent ligation of the coronary artery, is different from those using rats with myocardial ischemia followed by reperfusion, whereby estradiol could gain access to the ischemic tissue during the reperfusion phase.

Chronic administration of 17β-estradiol did not increase CO in the present study, but it was shown to increase CO in animals that did not have heart failure (24, 45). Estradiol reduced TPR as well as LVEDP, indicating reductions in preload and afterload. The former was the result of peripheral vasodilatation of resistance vessels and the latter was likely caused by venodilatation, because myocardial contractility was unaltered. It is of interest that captopril (an angiotensin-converting enzyme inhibitor) was shown to cause vasodilatation of capacitance vessels, which reduced LV preload, and vasodilatation of resistance vessels, which reduced afterload (28). Captopril is also well known to improve LV function and increase survival in heart failure.

The ovariectomized rats with chronic heart failure had attenuated depressor responses to ACh and SNP. Reduced vasodilator response to ACh has been reported in epicardial coronary artery of dogs with pacing-induced heart failure (39), in the perfused hindquarter of rats with chronic heart failure induced by ligation of the coronary artery (12), and in the forearm of patients with heart failure (21). Decreased depressor response to ACh is not necessarily indicative of decreased release of nitric oxide, because ACh has been shown to dilate resistance arteries primarily via the release of an endothelium-dependent hyperpolarizing factor (EDHF), which is distinct from nitric oxide or a prostanoi (for review, see Ref. 14). It has been suggested that impaired vasodilator response to ACh could be caused by abnormal production of cyclooxygenase-dependent vasoconstricting factor, impaired endothelial release of nitric oxide, and/or decreased vascular smooth muscle response to cGMP (18). Reduced response to cGMP likely contributed to reduced depressor response to ACh in this study, because responses to the nitrovasodilator SNP were also reduced in the rats with chronic heart failure. Moreover, attenuated epicardial coronary flow in response to nitroglycerin occurred in dogs with heart failure induced by pacing (39) or coronary embolization (20).

The ovariectomized rats with heart failure had insignificantly reduced pressor responses to NE and significantly reduced responses to l-NAME. However, attenuated contractile response to phenylephrine (α-adrenoceptor agonist) was observed in isolated, perfused mesenteric arteries from rats with heart failure elicited by ligation of the left coronary artery (34). Attenuated response to l-NAME suggests reduced involvement of nitric oxide in the regulation of vascular tone. Reduced pressor response to l-NAME has been reported in heart failure elicited by ventricular pacing in dogs (13) and sheep (27). Furthermore, there were reports of reduced nitrite release in isolated coronary arteries and microvessels from dogs with pacing-induced heart failure (39). Basal release of nitric oxide was, however, preserved in the perfused hindquarter of rats (12) and the radial artery of patients with congestive heart failure (11).
We found that chronic administration of 17β-estradiol to ovariectomized rats with heart failure did not alter pressor response to NE. There are no published studies on the chronic effects of estrogens on pressor responses to NE in animals with chronic heart failure. Chronic treatment with 17β-estradiol or mestranol did not alter pressor responses to NE in conscious, ovariectomized rats (32, 39). In contrast, chronic treatment of monkeys with estradiol attenuated pressor response to phenylephrine (45).

Chronic treatment of ovariectomized rats with 17β-estradiol further reduced depressor responses to ACh. It is unclear whether or not the attenuation was caused by reduced ACh-stimulated release of nitric oxide or the elusive EDHF. The former is possible if basal release of nitric oxide is already elevated by estradiol to near-maximal capacity. There are conflicting reports on the chronic effects of 17β-estradiol on vasodilator response to ACh. Chronic 17β-estradiol restored ACh-induced dilatation of atherosclerotic coronary artery in monkeys (43, 44), but it did not change the vasodilator response to ACh in the human forearm (36). 17β-Estradiol did not alter depressor responses to SNP, which suggests that the hormone does not restore the attenuated vasodilator response to nitric oxide or cGMP. There are also conflicting reports on the chronic effects of 17β-estradiol on vasodilatation response to nitrovasodilators. 17β-Estradiol potentiated SNP-induced forearm vasodilatation in women with risk factors for atherosclerosis and evidence for impaired vascular function (15) and nitroglycerin-induced vasodilatation in the brachial artery of male-to-female transsexuals (22). 17β-Estradiol attenuated SNP-induced vasodilator responses in coronary artery of cynomolgus monkeys (42) but did not affect SNP-induced coronary vasodilatation in atherosclerotic women (16).

Our finding of increased pressor response to L-NAME after chronic 17β-estradiol treatment in ovariectomized rats with heart failure is consistent with reports that estrogen increases the expression of nitric oxide synthase (41) and inhibits the production of superoxide (2) that inactivates nitric oxide. Furthermore, increased plasma levels of nitric oxide metabolites have been shown in dogs (19) and women (30) treated with 17β-estradiol.

Altered MAP responses to the various vasoactive drugs likely represent direct effects on blood vessels rather than varied baroreflex status of the animals. This is because all three groups of rats had subdied baroreflex activity during the hemodynamic study, as reflected by the insignificant regression relationship of HR on MAP in response to SNP and L-NAME. However, changes in baroreflex activity might have been missed because the rats were anesthetized with pentobarbital. Pentobarbital was shown to attenuate reflex changes in HR in response to L-NAME (40).

This study is the first to examine the effects of chronic 17β-estradiol on ovariectomized animals with chronic heart failure. Our results show that the restoration of serum 17β-estradiol has favorable cardiovascular actions through reductions in cardiac preload as well as afterload. Both reductions are likely a consequence of the restoration of the vasodilator role of nitric oxide by 17β-estradiol. These two actions should lead to reduced myocardial work and increased myocardial efficiency, which are of vital importance in heart failure. Our results indicate that hormone replacement therapy might have favorable cardiovascular actions in women with heart failure.

To summarize, our results indicate that ligation of the left main coronary artery in ovariectomized rats caused chronic heart failure characterized by decreased MAP, CO, LVEDP, and dP/dt, increased LVEDP, attenuated MAP responses to ACh, SNP, and L-NAME, and insignificant changes in TPR and responses to NE. Chronic treatment with 17β-estradiol reduced LVEDP and TPR, restored responses to L-NAME, further reduced depressor response to ACh but did not significantly alter other measured variables. Therefore, estrogen reduces preload as well as afterload and restores the vasodilator role of basal nitric oxide in ovariectomized rats with chronic heart failure.

This work and a studentship for A. A. Nekooeian were supported by the Heart and Stroke Foundation of British Columbia and Yukon.

Address for reprint requests: C. C. Y. Pang, Dept. of Pharmacology and Therapeutics, Univ. of British Columbia, 2176 Health Sciences Mall, Vancouver, BC, Canada V6T 2B3.

Received 11 November 1997; accepted in final form 23 February 1998.

REFERENCES

EFFECTS OF ESTROGEN IN CHRONIC HEART FAILURE.


