Effects of estrogen on venous function in rats with chronic heart failure

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Effects of estrogen on venous function in rats with chronic heart failure. Am J Physiol Heart Circ Physiol 278: H1941–H1947, 2000.—The effect of 17β-estradiol on venous function was investigated in ovariectomized rats with heart failure. Rats (50–60 days old) were ovariectomized and implanted with 60-day-release pellets that contain 17β-estradiol (1.5 mg) or vehicle. The left coronary artery was ligated 7 days later. Another group of ovariectomized rats was given vehicle pellets and then a sham operation was performed. The rats were studied while under pentobarbital anesthesia at 7 wk after ligation. Ligated rats, relative to sham groups, had lower mean arterial pressure (MAP, −34 mmHg) and cardiac output (CO, −38%); higher arterial resistance (R, +12%) and venous resistance (RV, +116%); mean circulatory filling pressure (MCFP, +40%) and left ventricular end-diastolic pressure (LVEDP, +11 mmHg); and similar cardiovascular responses to norepinephrine (NE). Treatment of ligated rats with 17β-estradiol increased CO (+16%); reduced RA (−16%), RV (−35%), MCFP (−23%), and LVEDP (−3 mmHg); and augmented MAP, RV, and MCFP responses to NE. Therefore, 17β-estradiol reduced MCFP, and this reduced preload (LVEDP). 17β-Estradiol decreased RV, which, along with decreased RA (afterload), led to an increase in CO. 17β-Estradiol likely augmented vasoconstriction to NE through an improvement on the cardiovascular status.

There are very few studies on the effect of estrogen on the cardiovascular function in animals with heart failure. We reported that the chronic administration of 17β-estradiol in rats with chronic heart failure reduced total peripheral resistance and left ventricular (LV) end-diastolic pressure (LVEDP) and augmented pressor response to Nω-nitro-L-arginine methyl ester (L-NAME, an inhibitor of nitric oxide synthase) (28). Estradiol, given chronically to rats with heart failure, also increased the ex vivo contractile response of the aorta, pulmonary artery, and portal vein to L-NAME (26). These results show that estradiol increases the vasodilator role of basal nitric oxide in heart failure. There are also limited studies on the effects of estrogen on venous function. The infusion of 17β-estradiol to women increased volume in the calf, indicating venodilatation (17). In addition, chronic administration of 17β-estradiol to ovariectomized guinea pigs increased mean circulatory filling pressure (MCFP) (11), the equilibrium circulatory pressure after an abrupt circulatory arrest (19, 38, 46); the increase was attributed to an increase in blood volume. Furthermore, chronic treatment of rabbits with 17β-estradiol enhanced ex vivo contractile response of the saphenous vein to norepinephrine (NE) (37).

Estrogen might exert its beneficial action in heart failure by improving venous function. There are, however, no published studies on the effect of estrogen on venous function in animals with heart failure despite knowledge of altered venous function in animals with acute or chronic heart failure. Both MCFP and venous resistance (RV) were elevated in dogs with acute heart failure induced by combined right ventricular pacing and volume loading (27, 31). MCFP was increased but RV was unaltered in dogs with pacing-induced chronic heart failure (32). MCFP was elevated and venous compliance was reduced in rats with chronic heart failure elicited by ligation of the left coronary artery (13, 35).

This study examined the chronic effect of estrogen replacement on venous function, namely, RV and MCFP, in ovariectomized rats with chronic heart failure elicited by ligation of the left main coronary artery.

MATERIALS AND METHODS

Implantation of pellets and ovariectomy. Age-matched (50–60 days old) female Sprague-Dawley rats were anesthetized with halothane and implanted subcutaneously with 60-day-release pellets containing vehicle or 17β-estradiol (1.5 mg) at the back of the neck. Afterward, an ovariectomy was per-
formed through a small midline incision on the skin at 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 this, bupivacaine (local anesthetic) and Cicalanin (bacitracin/neomycin powder) were applied to the wound, and the skin incision was closed. All animals were kept under 12 h of light and 12 h of darkness with standard rat chow and water ad libitum.

Coronary artery ligation. One week later, while under halothane anesthesia, vehicle-treated rats were given sham operation (V_S) or ligation of the left main coronary artery (V_CL). The 17β-estradiol-treated rats were given coronary artery ligation (E_CL). Briefly, a left thoracotomy was performed at the level of the fourth intercostal space, and the heart was exposed. The left main coronary artery was ligated at 2–4 mm from its origin using 6–0 prolene suture. In the sham-operated rats, the suture was passed through but the coronary artery was not ligated. Afterward, bupivacaine and Cicalan were applied, and the incisions were closed in layers. The rats then recovered from anesthesia.

Acute surgical preparation and instrumentation. Seven weeks after coronary ligation or sham operation, the rats were anesthetized with pentobarbital sodium (65 mg/kg ip). Polyethylene catheters (PE-50) were inserted into left and right iliac arteries and veins. The left and right iliac arteries were used for the measurement of mean arterial pressure (MAP) and withdrawal of reference blood samples (0.35 ml) for the determination of cardiac output (CO), respectively. Left and right iliac veins were respectively used for the measurement of central venous pressure (CVP) and administrations of vehicle, drugs, or 51Cr-labeled red blood cells for the measurement of blood volume. Another catheter was inserted into the left ventricle via the right carotid artery for the measurement of LVEDP and for the injection of 113Sn-labeled microspheres. A saline-filled, balloon-tipped catheter was inserted into the right atrium through the right jugular vein. When properly placed, inflation of the atrial balloon would stop circulation thereby causing a decrease of MAP to 20–25 mmHg within 5–7 s. MAP, LVEDP, and CVP were recorded with a pressure transducer (PD 23B Gould Statham) connected to a Grass polygraph (model PR57C8B). The rate of rise of LV pressure (+dP/dt) was quantified using an electronic differentiator (model 7P20C; Grass). Heart rate (HR) was counted from the upstroke of the arterial pulse pressure. All catheters were filled with heparinized normal saline (25 IU/ml). 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). Rats were used 1 h after the surgery was completed.

Experimental protocol. Six groups of rats (n = 6 each) consisting of two groups each of ovarioectomized V_S, V_CL, and E_CL rats were used. After stabilization, a blood sample (0.6 ml) was taken from each rat for the measurement of serum 17β-estradiol, blood volume, and hematocrit. Baseline cardiovascular measurements were also taken at this time. Afterward, one group each of V_S, V_CL, and E_CL was given normal saline (0.018 ml/min), and the other group was given NE (0.5 μg·kg⁻¹·min⁻¹). At 15 min following the start of infusion of saline or NE, cardiovascular variables were again measured. At the end of the experiments, the rats were euthanized, lungs and ventricles were dissected out and weighed, and myocardial infarcts were quantified.

Another group (n = 12) of age-matched intact rats not implanted with pellets was anesthetized with pentobarbital and catheterized for venous blood sampling to allow the measurement of control serum concentration of 17β-estradiol.

Assessment of surface area of infarct. A modified method of Chien et al. (8) was used to quantify the infarcted area. Briefly, after the atria was cut away, the ventricle was cleaned of blood, and a saline-filled balloon was inserted into the left ventricle. The balloon was inflated and sealed, and the heart was placed in 10% 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, the right ventricle was trimmed away, and an incision was made in the left ventricle so that the tissue could be flattened and traced. The circumference of the left ventricle 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, and this was estimated by the proportional weights of the respective areas marked on the plastic sheet.

Measurement of serum 17β-estradiol. The blood samples were clotted for >30 min and centrifuged at 10,000 rpm for 10 min to separate the serum, which was stored at −20°C. Serum concentrations of estradiol were quantified using a 125I-labeled radioimmunoassay kit (ICN Biomedicals, Costa Mesa, CA). The intra-assay and interassay coefficients of variation were 4.7 and 9.1%, respectively, and the limit of detection of the assay was 10 pg/ml. All samples, including the standard curve, were run in duplicate, and the average is reported.

Blood volume and cardiac output measurements. Blood volume was measured using the radioactively labeled red blood cell technique (12). Briefly, 51Cr (Amersham)-labeled red blood cells (0.3 ml) were intravenously injected as a bolus. Five minutes later, blood (0.3 ml) was withdrawn from the LV catheter and counted for radioactivity. CO was measured by the injection of 113Sn-labeled microspheres (25,000–30,000 spheres, 15 μm diameter, New England Nuclear) and removal of a reference blood sample (49). A Searle 1185 series dual channel automatic gamma counter was used for the counting of radioactivity.

Drugs. Pellets containing 17β-estradiol or vehicle were obtained from Innovative Research of America (Sarasota, FL). Norepinephrine bitartrate was obtained from Sigma Chemical (St. Louis, MO) and dissolved in normal saline (0.9% NaCl).

Calculations and statistical analysis. Red blood cell volume (RCV), plasma volume (PV), blood volume (BV), CO, arterial resistance (R_a), MCFP, pressure gradient for venous return (PGVR), and R_V were calculated as follows:

\[
RCV (ml) = \frac{\text{injected radioactivity (cpm)} \times \text{Hct}}{\text{cpm/ml of withdrawn blood sample} \times 100}
\]

\[
BV (ml) = \frac{RCV (ml) \times 100}{\text{Hct}}
\]

\[
PV (ml) = BV (ml) - RCV (ml)
\]

\[
CO (ml/min) = \frac{\text{rate of withdrawal of blood (ml/min)} \times \text{total injected cpm}}{\text{cpm in withdrawn blood}}
\]
The effects of NE or vehicle on cardiovascular variables were calculated as changes from preinfusion values. All data were analyzed by ANOVA followed by Duncan’s multiple range test and are presented as means ± SE. The results of NE on MAP were logarithm-transformed before statistical analysis to obtain homogeneity of variance. A P value of < 0.05 was taken as the criterion for statistical significance.

RESULTS

Serum estradiol. Serum concentration of 17β-estradiol in intact rats was 213 ± 24 pg/ml (n = 12). This value represents the average concentration of the hormone in the rats at different stages of the estrus cycle. Ovariectomy reduced it to 100 ± 7 and 99 ± 5 pg/ml, respectively, in the sham-operated rats (n = 12) and in coronary artery-ligated rats treated with vehicle (n = 12). Treatment of coronary artery-ligated rats (n = 12) with 17β-estradiol restored serum 17β-estradiol to 223 ± 9 pg/ml.

Baseline measurements. Because there were no significant differences in any of the baseline measurements between the two groups each of sham-operated rats treated with the vehicle, coronary artery-ligated rats treated with the vehicle, or coronary artery-ligated rats treated with 17β-estradiol, the values for the two groups with the same treatments were pooled (Tables 1 and 2). There was no myocardial infarct in sham-operated rats treated with the vehicle. Ligation of the coronary artery produced similar surface areas of infarct in rats treated with the vehicle or 17β-estradiol. Relative to sham-operated rats, coronary artery-ligated rats treated with the vehicle had increased wet lung weight and similar body or ventricular weight. Relative to coronary artery-ligated rats treated with the vehicle, the ligated rats treated with 17β-estradiol had similar ventricular weight but reduced lung weight and body weight. Relative to sham-operated rats, the vehicle-treated ligated rats had increased red blood cell volume, plasma volume, and blood volume but similar hematocrit. Relative to vehicle-treated ligated rats, 17β-estradiol-treated coronary-ligated rats had decreased hematocrit and red blood cell volume, increased plasma volume but similar blood volume (Table 1).

Compared with sham-operated rats treated with vehicle, coronary artery-ligated rats treated with vehicle had lower MAP, CO, LV + dP/dt, higher RA, LVEDP, MCPF, CVP, PGVR, and RV, and similar HR (Table 2). Relative to treatment with the vehicle, treatment of coronary artery-ligated rats with 17β-estradiol reduced RA, LVEDP, MCPF, CVP, PGVR, and RV, and increased CO but did not alter MAP, LV + dP/dt, or HR (Table 2).

Cardiovascular effects of NE. Saline did not alter any of the cardiovascular variables (Figs. 1–3). Infusion of NE into sham-operated rats treated with the vehicle increased MAP, CO, LV + dP/dt, PGVR, MCPF, and RV but did not significantly alter RV or LVEDP (Figs. 1–3). NE caused similar cardiovascular responses in coronary artery-ligated rats treated with vehicle as in sham-operated rats (Figs. 1–3). Treatment of coronary artery-ligated rats with NE had lower MAP, CO, LV + dP/dt, higher RA, LVEDP, MCPF, CVP, PGVR, and RV, and increased CO but did not alter MAP, LV + dP/dt, or HR (Table 2).

Table 1. Baseline measurements of surface areas of myocardial infarct, ventricular, wet lung and body weights, hematocrit, as well as red blood cell, plasma and blood volumes in vehicle-treated and 17β-estradiol-treated sham-operated rats and coronary-ligated rats

<table>
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<tr>
<th></th>
<th>VA</th>
<th>VC</th>
<th>EL</th>
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<tr>
<td>Infarct area, %</td>
<td>33 ± 1</td>
<td>32 ± 1</td>
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<tr>
<td>Ventricular weight, g</td>
<td>0.95 ± 0.02</td>
<td>0.96 ± 0.02</td>
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<tr>
<td>Wet lung weight, g</td>
<td>1.35 ± 0.02</td>
<td>1.88 ± 0.10*</td>
<td>1.35 ± 0.02†</td>
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<tr>
<td>Body weight, g</td>
<td>322 ± 8</td>
<td>318 ± 10</td>
<td>269 ± 10†</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>47 ± 1</td>
<td>47 ± 1</td>
<td>41 ± 1†</td>
</tr>
<tr>
<td>Red blood cell volume, ml</td>
<td>7.8 ± 0.2</td>
<td>9.8 ± 0.4*</td>
<td>8.1 ± 0.5†</td>
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<tr>
<td>Plasma volume, ml</td>
<td>8.9 ± 0.3</td>
<td>10.2 ± 0.4*</td>
<td>11.5 ± 0.4†</td>
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<tr>
<td>Blood volume, ml</td>
<td>16.7 ± 0.5</td>
<td>20.0 ± 0.6*</td>
<td>19.6 ± 0.8*</td>
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Values are means ± SE; n = 12 rats. VA, sham-operated vehicle; VC, coronary-ligated vehicle; EL, coronary-ligated vehicle treated with 17β-estradiol. *Significantly (P < 0.05) different from VA. †Significantly different from VC.

Table 2. Baseline variable measurements in vehicle-treated sham-operated rats and in vehicle-treated or 17β-estradiol-treated coronary-ligated rats

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<tr>
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<th>VA</th>
<th>VC</th>
<th>EL</th>
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<tr>
<td>MAP, mmHg</td>
<td>112 ± 2</td>
<td>78 ± 4*</td>
<td>75 ± 3†</td>
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<tr>
<td>CO, ml/min</td>
<td>89 ± 2</td>
<td>55 ± 2*</td>
<td>64 ± 2†</td>
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<tr>
<td>RA, mmHg·min·ml⁻¹</td>
<td>1.28 ± 0.04</td>
<td>1.43 ± 0.03*</td>
<td>1.20 ± 0.06†</td>
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<tr>
<td>HR, beats/min</td>
<td>338 ± 7</td>
<td>353 ± 6</td>
<td>337 ± 6</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>−3.3 ± 0.6</td>
<td>8.0 ± 0.9*</td>
<td>4.8 ± 0.5†</td>
</tr>
<tr>
<td>+dP/dt, mmHg/s</td>
<td>4,542 ± 74</td>
<td>3,146 ± 129*</td>
<td>3,250 ± 115*</td>
</tr>
<tr>
<td>MCPF, mmHg</td>
<td>5.2 ± 0.1</td>
<td>7.3 ± 0.2*</td>
<td>5.6 ± 0.2†</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>1.9 ± 0.1</td>
<td>2.9 ± 0.2*</td>
<td>2.3 ± 0.2†</td>
</tr>
<tr>
<td>PGVR, mmHg</td>
<td>3.0 ± 0.2</td>
<td>4.5 ± 0.4*</td>
<td>3.0 ± 0.2†</td>
</tr>
<tr>
<td>RV, mmHg·min·ml⁻¹</td>
<td>0.037 ± 0.002</td>
<td>0.080 ± 0.003*</td>
<td>0.052 ± 0.004†</td>
</tr>
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Values are means ± SE; n = 12 rats. MAP, mean arterial pressure; CO, cardiac output; RA, arterial resistance; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; +dP/dt, rate of rise of LV pressure; MCPF, mean circulatory filling pressure; CVP, central venous pressure; PGVR, pressure gradient for venous return; RV, venous resistance. *Significantly (P < 0.05) different from VA. †Significantly different from VC.
artery-ligated rats with 17β-estradiol augmented the effects of NE on MAP, PGVR, MCFP, and RV, and insignificantly increased NE responses on RA and CO but did not alter NE effects on the other measurements (Figs. 1–3).

DISCUSSION

Serum 17β-estradiol was reduced by ovariectomy to half that of age-matched intact rats; the latter measurements were not timed at any specific stage of the estrus cycle. The sustained-release pellets restored serum estradiol to a concentration similar to that of intact rats. Because rats have their first estrus cycle at 37 days of age (2), the rats in the present study were ovariectomized at 13–23 days postestrus. Therefore, estrogen treatment represented a replacement therapy.

The results show that ligation of the coronary artery in rats caused chronic heart failure characterized by reduced MAP (−30%), CO (−38%), and LV + dP/dt (−31%), and increased RA (+12%), LVEDP (+11 mmHg), and wet lung weight (+39%) at 7 wk after coronary ligation. These changes are consistent with those previously reported in rats with chronic heart failure elicited by coronary ligation (13, 35, 39). In addition, the rats with coronary ligation, relative to sham-operated rats, had increased MCFP (+40%), PGVR (+48%), and RV (+116%). These venous values are also in general agreement with those reported previously for animals with acute or chronic heart failure elicited by coronary ligation or right ventricular pacing. After coronary ligation, MCFP was increased by 29% in conscious rats with myocardial infarction (13) and by 21 and 65% in anesthetized rats with small and large infarcts, respectively (35). MCFP was increased by 117% in anesthetized dogs with acute heart failure induced by volume overload plus pacing (27) and by 87% in anesthetized pigs with pacing-induced chronic heart failure (30). MCFP and RV were increased by 18 and 90%, respectively, in anesthetized rats with acute heart failure caused by coronary ligation (29).

Relative to the values in sham-operated rats, blood volume (+20%), plasma volume (+15%), and red blood cell volume (+26%) increased, and hematocrit remained unchanged at 7 wk after ligation. Blood and plasma volumes were reported to be increased (35), but hematocrit remained unchanged (13, 35) in the coronary artery ligation model of chronic heart failure.
Similar to our previous observations (26, 28), 17β-estradiol reduced arterial resistance (−16%) and LVEDP (−40%) but did not alter MAP, LV dP/dt, or surface area of myocardial infarction in the rats with coronary occlusion. There are no published reports on the effect of estrogen on venous function in animals with chronic heart failure. In this study, chronic 17β-estradiol reduced MCFP (−23%) and PGVR (−33%) in rats with heart failure. In the absence of a change in blood volume, a reduction in MCFP reflects a decrease in venous compliance (18), and this leads to a reduction of PGVR, the driving pressure for venous return. Chronic 17β-estradiol treatment, however, also reduced $R_V$ (−35%) in rats with heart failure, indicating the dilatation of venous resistance vessels. Reduced $R_V$ would increase venous return and thereby oppose the effect of reduced PGVR. Venous return, as reflected by CO, was increased by estradiol, and this was likely due to the concurrent dilatation of arterial resistance vessels through a reduction in $R_A$ (−16%). 17β-Estradiol was also found to reduce (−13 to −18%) $R_A$ in our previous studies (26, 28). It is of interest that estradiol caused substantially greater dilator action in venous than arterial resistance vessels.

In the present study, 17β-estradiol increased CO (+16%) in rats with chronic heart failure. Estradiol also increased CO (+9 to +13%) in our previous studies; however, the increases did not reach statistical significance due to the smaller sample sizes in these studies (26, 28). Estradiol has been shown to increase CO in animals without heart failure (22, 50) as well as in male transsexuals (41). The increase of CO by 17β-estradiol in this study was primarily due to reductions in flow resistances $R_A$ and $R_V$, because neither HR nor cardiac contractility (LV $+dP/dt$) was altered, and PGVR was reduced. The dilatation of $R_A$ vessels would diminish afterload, the impedance to cardiac ejection, thereby reducing workload as well as oxygen consumption of the failing heart. Reduced MCFP would reflect increased venous compliance (18) and would be expected to shift blood volume from the central circulation to the peripheral venous system (33, 48) thereby reducing ventricular preload, systolic wall tension, and myocardial oxygen consumption (42). Indeed, preload (LVEDP) was reduced by estradiol in the present study, and this could have been the results of reduced ventricular compliance, afterload, as well as venous compliance.

There are no published studies on the mechanism by which 17β-estradiol causes venodilatation. Pretreatment with glibenclamide attenuated 17β-estradiol-induced vasodilatation of the canine epicardial coronary artery in vivo (45), indicating the possible involvement of ATP-sensitive K⁺ channels for the dilator effect of 17β-estradiol. 17β-Estradiol also relaxed precontracted arterial rings in vitro (5, 6, 20) via the blockade of Ca²⁺ channels (20). Moreover, 17β-estradiol increased the release of endothelium-derived nitric oxide (24) and formation of cAMP as well as cGMP (25). Nitric oxide is likely a venodilator in vivo, because inhibitors of nitric oxide synthase have been shown to increase MCFP in conscious rats (16) and $R_V$ in anesthe-

Treatment with 17β-estradiol reduced red blood cell volume (−17%) and hematocrit (−16%) and further increased plasma volume (+13%) but did not change blood volume. The lack of a change in blood volume by 17β-estradiol was the result of a decrease in red blood cell volume and an increase in plasma volume. Chronic treatment with 17β-estradiol has been shown to increase plasma volume in sheep (22, 47) and guinea pigs (11) that did not have heart failure, reduced red blood cell volume in male transsexuals (41), and decreased hematocrit in sheep (11, 22, 47).

It is unclear how 17β-estradiol, given chronically, increased plasma volume and decreased red blood cell volume. The increase in plasma volume by estradiol could be due to increased release of arginine vasopressin and/or Na⁺ retention. There are, however, conflicting reports on the chronic effect of estradiol on arginine vasopressin release and plasma osmolality; the divergent results could be due to variations in the dose, mode, and duration of estradiol treatment and the experimental conditions (4, 34, 43).
tized rats (49). The venodilator action of 17β-estradiol in animals with heart failure might have been the combined effects of increased release of nitric oxide, opening of ATP-sensitive K+ channels, and blockade of Ca2+ channels.

NE did not alter Rv or LVEDP but caused similar increases in MAP, CO, LV +dP/dt, PGVR, MCFP, as well as RV in vehicle-treated, sham-operated rats and coronary-ligated rats. Treatment with 17β-estradiol enhanced MAP, PGVR, MCFP, and RV but not LVEDP or LV +dP/dt responses to NE. The estradiol-induced increase in MAP response to NE was due to increases in RA and CO; however, neither of these increases reached statistical significance. Estradiol enhanced pressor response to NE in rat mesenteric arteries in vivo (1). The mechanism by which 17β-estradiol increased vasconstrictor response to NE is unclear. 17β-Estradiol was reported to decrease the release of NE (7) as well as increase the affinity (9) and density (9, 36) of β1-adrenoceptors. Therefore, it is tempting to speculate that 17β-estradiol might have enhanced responses to NE in the arterial and venous circulation by decreasing the release of NE leading to the upregulation of β1-adrenoceptors. Contrary to the present findings, treatment with 17β-estradiol pellets (50 µg) for 21 days (10) or mestranol (15 µg/day ip biweekly) for 4 to 6 wk (40) did not alter pressor responses to intravenous bolus injections of NE in conscious, ovariectomized rats. Moreover, acute intramuscular injection of 17β-estradiol (10 mg) in healthy men did not affect constrictor responses to intravenous bolus injections of NE in superficial hand veins (21). Discrepancies in responses to NE among various studies might be due to differences in the dose and/or duration of estrogen therapy, methods of NE administration, and the pathophysiologic state of the animals (healthy vs. chronic heart failure).

To summarize, our results show that ligation of the coronary artery in ovariectomized rats resulted in chronic heart failure characterized by lower MAP, CO, and LV contractility as well as higher RA, LVEDP, MCFP, PGVR, and RV relative to the corresponding values in sham-operated rats. Coronary artery ligation did not alter cardiovascular responses to NE. Chronic replacement of 17β-estradiol in ovariectomized rats with heart failure increased CO and reduced RA, LVEDP, PGVR, MCFP, and RV, reflecting the dilatation of resistance as well as capacitance vessels. Furthermore, 17β-estradiol augmented the constrictor responses to NE in the arterial as well as venous system.

Perspectives. Estrogen replacement in ovariectomized rats with chronic heart failure increased CO through reductions in arterial as well as venous resistances and reduced LVEDP, PGVR, and MCFP in the present study. Reductions in LVEDP and arterial resistance indicate the reductions in preload and afterload, respectively, and this should lead to reduced myocardial work and increased myocardial efficiency, which are of vital importance in heart failure. The cardiovascular profile of estradiol is similar to that of captopril (inhibitor of angiotensin-converting enzyme), which has been shown to cause the vasodilatation of arterial resistance vessels as well as capacitance vessels in rats with myocardial infarction through a reduction in MCFP and an increase in venous compliance (35). Captopril is well known to improve LV performance and increase survival in heart failure. Interestingly, captopril has no venodilator action in rats without myocardial infarction. Our study is the first that demonstrates a prominent venodilator action of estrogen in rats with heart failure. It should be important to find out if estrogen has a similar venodilator action in other animals or models of heart failure, and if it affects venous function of animals without heart failure.

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