Acute effects of 17β-estradiol on ventricular and vascular hemodynamics in postmenopausal women

CHRISTOPHER S. HAYWARD,1,2 WALLY V. KALNINS,1 AND RAYMOND P. KELLY1
1Department of Cardiology, St. Vincent’s Hospital, Sydney 2010, Australia; and 2Department of Cardiac Medicine, National Heart and Lung Institute, Imperial College, London SW3 6LY, United Kingdom

Received 3 January 2000; accepted in final form 28 April 2000

Hayward, Christopher S., Wally V. Kalnins, and Raymond P. Kelly. Acute effects of 17β-estradiol on ventricular and vascular hemodynamics in postmenopausal women. Am J Physiol Heart Circ Physiol 279: H2277–H2284, 2000.—Because premenopausal women have lower cardiovascular morbidity than postmenopausal women, it has been proposed that estrogen may have a protective role. Estrogen is involved in smooth muscle relaxation both through its specific receptor as well as through calcium channel blockade. This study examined the acute effect of estradiol on invasive cardiovascular hemodynamics in 18 postmenopausal women (age 62.6 ± 7.6 years, means ± SD). The effect of estradiol on left ventricular chamber performance was studied in 9 women using simultaneous left ventricular pressure-volume recordings. In a further group of 9 women, the acute effect of estradiol on arterial function was assessed using input impedance (derived from simultaneous aortic pressure and flow recordings), pressure waveform analysis, and pulse wave velocity. After 2 mg micronized 17β-estradiol was administered, serum estradiol levels increased from 50.9 ± 21.9 to 3,190 ± 2,216 pmol/l, P < 0.0001. There was no effect of estradiol on either left ventricular inotropic or lusitropic function. There was no acute effect of estradiol on arterial impedance, reflection coefficient, augmentation index, or pulse wave velocity. There was a trend to decreased heart rate and cardiac output in both groups of 9 women. Because heart rate and cardiac output were common to both hemodynamic data sets, results for these parameters were pooled. Across all 18 women, there was a small but significant decrease in heart rate (69.2 ± 10.4 vs. 67.2 ± 9.9 beats/min, P = 0.02), as well as a significant decrease in cardiac output (4.82 ± 1.77 vs. 4.17 ± 1.56 l/min, P = 0.002). Despite achieving supraphysiological serum levels, this study found no significant effect of acute 17β-estradiol on ventricular or large artery function.

Methods

Patients

Eighteen postmenopausal women (defined by history of amenorrhea and subsequent serum estradiol <105 pmol/l) were recruited from those undergoing elective cardiac catheterization. The Research Ethics Committee of St. Vincent’s Hospital approved the study, and all patients gave written informed consent. The acute effects of estradiol on left ventricular (LV) chamber function were examined in nine women, and its effects on arterial impedance and pulse wave velocity were examined in a further group of nine women. The mean age of the cohort was 62.6 ± 7.6 (±SD) years, and mean body mass index was 26.6 ± 5.0 kg/m². Fourteen subjects had no significant coronary artery disease, two had double vessel disease, and two had triple vessel disease. All subjects had normal global LV function (ejection fraction >50%), although one subject had minor inferior hypokinesis on ventriculography. There was no difference in effect between those with no coronary disease and the remaining few, so results are presented for the entire cohort. Two subjects were diabetic and ten had a history of treated hypertension. Patients were studied on their usual medication. Current medications included β-blockers in four subjects, calcium channel antagonists in five, angiotensin-converting enzyme inhibitors in six. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Because women have lower cardiovascular morbidity and mortality until the time of the menopause (13, 20, 31), it has been speculated that hormones may play an important cardioprotective role. It has been shown that estrogen has beneficial effects on coronary vasomotion (40), through endothelial production of nitric oxide (7).
inhibitors in five, isosorbide mononitrate in three subjects, and diuretics in two subjects. Of the entire cohort, nine were taking long-acting vasodilators (angiotensin-converting enzyme inhibitors, calcium antagonists, or isosorbide mononitrate) administered on the morning of the study. Hemodynamic study was performed ∼3 h postdose.

**Estradiol Administration Protocol**

All subjects had baseline hemodynamic recordings and serum estradiol assays taken before sublingual estradiol was given. Estradiol assays were taken from arterial blood from the femoral sheath. Subjects were then given crushed micronized 1 mg 17β-estradiol (Trisequens, Novo Nordisk, Denmark) sublingually with a sip of water. LV pressure volume and aortic pressure-flow recordings were taken for 10 min and then a further 1-mg micronized estradiol was given by the same route. Recordings were continued for a further 10 min, at which time the second estradiol assay was taken. This protocol was used prospectively to allow delineation of any acute (10 min) estradiol effect at the lower dose. Serum for estradiol levels was taken at the commencement of the recordings and after completion of the 20-min protocol.

**Data Acquisition**

Pressure-volume loops LV pressure-volume (PV) loops were obtained by simultaneous measurement of LV pressure (micromanometer) and volume (conductance method) as has been previously described (9). Briefly, an 8-Fr. conductance volume catheter (9 mm electrode spacing, Webster 7212–08, Webster Lab) was inserted into the LV cavity via a femoral arterial sheath under fluoroscopic control. The micromanometer was then inserted to the tip of the volume catheter and connected for data acquisition. Volume signals were processed via a Leycom signal conditioner (Sigma 5, Cardiodynamics, Rijnsburg, Netherlands) to a data acquisition board in a portable computer (Intel 486 processor, DX50). Data were displayed on-line at a sampling rate of 250 Hz with high-frequency, noise-filtering cut-off at 50 Hz, 20 dB/decade. Data were automatically determined from the averaged PV loop by custom software (PVAN, Pressure-Volume Analysis, Johns Hopkins University, Baltimore, MD). Steady-state parameters included heart rate, cardiac output, LV systolic pressure, end-diastolic pressure (pre a wave), peak positive pressure development over time (dP/dt max), peak negative dP/dt (dP/dt min), time constant of relaxation (T), duration of contraction, and end-systolic pressures and volumes. For the purposes of steady-state diastolic parameters, the point of end diastole was determined separately using pressure derivatives to calculate the pressure and volume immediately before the atrial filling wave. End systole was defined by the maximum of time-varying ventricular elastance (E′ s) as described by the equation $E'_s = \frac{P}{V}$ where $V$ is the volume axis intercept as defined below. Tau was determined using a logarithmic least-squares regression commencing at peak dP/dt max and extending for a further 80 ms. Duration of electromechanical systole was defined from the midpoint of the electrocardiographic QR wave to dP/dt min. This measure was used as a measure of duration of contraction.

**Chamber function**

The load-independent indexes end-systolic PV relations (ESPVR), preload-recruitable stroke work relations (PRSWR), and end-diastolic PV relations (EDPVR) were obtained during transient IVCO. Because linear relationships were assumed for all indexes, individual IVCO runs with a linear correlation of <0.80 were not included in analysis. For ESPVR, an iterative procedure was performed from the linear regression of the data using an initial estimate of $V_0$, V0 of 0 ml. Subsequent iterations were continued until errors were minimized as previously described (18). Because of poor correlations in individual runs or ventricular ectopy in response to IVCO, some studies were found to be unsuitable for load-independent analyses. 

End-diastolic relationships were determined from two EDP/EDV points on each PV loop. The points chosen were those immediately before the a wave and a second point 10% of the filling volume earlier in the same loop as has been described previously (21). By examining diastole before atrial contraction, this provides an assessment of the passive diastolic properties of the left ventricle. A linear model was used to describe the EDPVR because this is simpler and has been shown to be as valid as more complex exponential regression models (16). Although the slope of the regression describes an elastance, the results are usually reported as the inverse, namely chamber compliance $C_{Dia}$ (17). The equation for diastolic compliance is therefore $V = C_{Dia}P + V_{0dil}$ where $V_{0dil}$ is the volume axis intercept.
**Arterial parameters.** Because of problems with flow catheter positioning and flow waveform, impedance results were only available for seven of the nine subjects. Problems with the Finapres device and with the femoral pressure trace in two separate patients meant that pulse wave velocity and aorto-femoral transfer function results were available for seven of the nine patients. Data were averaged from steady-state recordings. Pressure, flow, and Finapres waveforms were ensemble averaged using electrocardiogram triggering to obtain an averaged waveform before entry into a discrete Fourier transform calculation to determine impedance and transfer functions. Individual impedance and transfer function results were derived from the ratio of the Fourier components of the aortic pressure to corresponding aortic flow and femoral pressure, respectively. Sampling rate was 250 Hz for all channels. The last one-third of the flow waveform was assumed to be zero and was used to autocalibrate for offset drift. Results for frequency-dependent parameters were reported up to the tenth harmonic, beyond which the signal-to-noise ratio is too low for meaningful analysis. Characteristic impedance \( Z_c \) was defined as the mean of impedance modulus for harmonics 4–10.

Time domain parameters such as augmentation index (19), reflection wave ratio (37), and ejection duration were derived using pressure derivatives. Whereas augmentation index is defined by the ratio of the difference between the late and early systolic shoulders to the aortic pulse pressure, the reflection wave ratio uses the ratio of the height of the late to early pressure peaks from the pressure waveform. The indexes are similar in the information derived from them. Pulse onset for pulse wave velocity calculation was determined using the peak of the second derivative. Distances were determined from the sternal notch to femoral transducer tip and from the sternal notch to Finapres cuff by surface anatomy.

Systemic vascular resistance was calculated using the ratio of the mean aortic pressure to cardiac output multiplied by 80 (to convert to units of dyn·s·cm\(^{-2}\)). This assumes a right atrial pressure of zero, which may lead to a minor overestimation of systemic vascular resistance. Reflection coefficient \( \Gamma \) was calculated according to \( \Gamma = (Z_t - Z_c)/(Z_t + Z_c) \), where \( Z_t \) is the terminal impedance, and \( Z_c \) the characteristic impedance. Absolute Finapres pressures were not found to be reliable and were not further analyzed. The Finapres waveform was used solely for timing purposes for calculation of brachial pulse wave velocity.

**Statistics**

Results are shown as means ± SD. The effect of estradiol on steady-state parameters was analyzed using paired \( t \)-tests. To determine the effect of estradiol on chamber function (ESPVR, EDPVR, PRSWR), a multiple linear regression model was used coding for the effect of estrogen on both the slope and intercept of the appropriate relationship after accounting for the baseline differences between individuals using dummy coding (34).

**RESULTS**

**Estradiol Levels**

Serum estradiol levels increased in all subjects. The smallest change in serum estradiol level in any subject was a greater than fivefold increase in concentration, from 92 to 548 pmol/l. In the entire cohort estradiol levels increased from 50.9 ± 21.9 to 3,190 ± 2,216 pmol/l, \( P < 0.0001 \).

**Estradiol and LV Chamber Function**

**Steady-state recordings.** Baseline steady-state parameters and results for the last 5 min of the study are shown in Table 1. Interim analysis revealed no effect of estradiol at 10 min. It is of note that, despite marked elevation of the serum estradiol level, no change in blood pressure or ejection fraction were found. There was a trend to decreased heart rate and cardiac output. There was no evidence for any lusitropic effect, as shown by either tau or \( dP/dt_{\text{min}} \). There was no change in arterial elastance, suggesting no marked change in arterial or arteriolar tone. Indeed, arterial elastance tended to increase in this study (\( P = 0.19 \)).

**LV chamber function.** Systolic function was assessed using ESPVR and PRSWR (Table 2). There was no inotropic effect of estradiol (\( P = 0.59 \) and 0.51, respectively). An example of PV loops before and at the end of the study period is shown in Fig. 1. As can be seen in this patient, there was no significant change in LV contractility due to estradiol. Passive diastolic ventric-
ular function was assessed by examining EDPVR. Again, there was no effect of estradiol administration on chamber distensibility ($P = 0.68$).

**Estradiol and Arterial Hemodynamics**

**Baseline parameters.** There was a statistically significant, but small, decrease in heart rate (69.8 ± 9.4 vs. 66.0 ± 6.9 beats/min, $P < 0.05$) from baseline to 10 min; however, overall heart rate had not changed significantly from baseline at the end of the study period ($P = 0.12$). Whereas there was no change in any pressure-related parameter, there was a significant decrease in cardiac output and peak aortic flow velocity with time (Table 3). Calculated systemic vascular resistance increased significantly over the first 10 min of the study period, with a trend to increased vascular resistance remaining at the end of the study period ($P = 0.06$). Tau (arterial) derived from an exponential decay model of the aortic pressure waveform (windkessel model) tended to suggest a decrease in aortic compliance ($P = 0.07$).

**Aortic input impedance.** Analysis of impedance spectra showed no significant changes at any harmonic (Fig. 2). $Z_t$ (impedance at zero frequency = systemic vascular resistance) increased significantly in the interim time period but was not significantly different by the end of the study. $Z_t$ did not change significantly in response to estradiol (Table 3). Because the small changes in $Z_t$ were in a similar direction to those in $Z_c$, there was no significant change in the calculated $\Gamma$.

**Pulse waveform analysis and pulse wave velocity.** The aortic augmentation index and reflection wave ratios were used as further markers of peripheral arterial wave reflection. There was no significant change in systolic augmentation, ejection duration, or pulse wave velocity at any time during the study (Table 3). Consistent with other studies in older subjects, the aortic pulse wave velocity was greater than brachial.

**Aorto-femoral transfer function.** To further delineate any change in arterial function, as may be expected by smooth muscle relaxation, the aorto-femoral transfer function was derived for each time period. There was a characteristic amplification of lower frequencies with diminution of higher harmonics (Fig. 2). This is similar to that seen in brachial and radial transfer functions (14). The phase decreases in an approximately linear manner in accordance with the delay between the two pulses due to transit delay. There was no significant change in either amplification or phase delay over the first 10 min. At 20 min, there was a small but significant decrease in mean femoral arterial pressure, as shown by a decrease in amplification at zero frequency.

![Fig. 1. Example of a series of pressure-volume (PV) loops during inferior vena caval occlusion (IVCO) in a single patient used in derivation of the end-systolic PV relationship (ESPVR) before estrogen (solid line, open circles) and at study completion, 20 min after estrogen (dotted line, filled circles). As can be seen, ESPVR did not change. LV, left ventricular.](http://ajpheart.physiology.org/)
at 20 min (Fig. 3). This may have been due to intraluminal thrombus deposition with time, despite regular flushing, due to the close fit of the pressure-flow catheter within the arterial sheath. There was no change in mean aortic pressure (Table 3). There were no changes in phase delays due to estradiol administration.

Pooled data. Because heart rate and cardiac output were common to the two studies, analysis could be performed across all 18 subjects, increasing statistical power. Across all 18 subjects, there was a small, but significant, decrease in heart rate across the study period (from 69.2 ± 10.4 to 67.2 ± 9.9 beats/min, P = 0.02). Cardiac output was derived by stroke volume in the ventricular study (n = 7) and by integrated aortic flow velocity (n = 7) in the impedance study. Because the results were compared using paired t-tests, this was not considered a barrier to appropriate interpretation of the results. There was a significant decrease in cardiac output across the entire group (from 4.82 ± 1.69 to 4.17 ± 1.56 l/min, P = 0.002). From the variability in increase in serum estradiol levels, the relation between either change in estradiol levels or absolute estradiol levels was also examined. There was no relationship (P = 0.68–0.83) between either the percentage change in estradiol level or absolute estradiol level and changes in either heart rate or cardiac output.

Table 3. Effect of estradiol on resting hemodynamics in patients undergoing pressure-flow recordings

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Baseline</th>
<th>SD</th>
<th>Estradiol</th>
<th>SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hemodynamics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>9</td>
<td>69.8</td>
<td>6.9</td>
<td>67.2</td>
<td>7.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Aortic systolic pressure, mmHg</td>
<td>9</td>
<td>131.6</td>
<td>20.0</td>
<td>130.8</td>
<td>22.6</td>
<td>0.72</td>
</tr>
<tr>
<td>Aortic diastolic pressure, mmHg</td>
<td>9</td>
<td>66.3</td>
<td>7.1</td>
<td>67.1</td>
<td>7.1</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean aortic pressure, mmHg</td>
<td>9</td>
<td>93.9</td>
<td>10.8</td>
<td>94.3</td>
<td>12.9</td>
<td>0.80</td>
</tr>
<tr>
<td>Peak flow velocity, cm/s</td>
<td>7</td>
<td>73.4</td>
<td>26.5</td>
<td>67.2</td>
<td>26.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
<td>7</td>
<td>5.54</td>
<td>2.00</td>
<td>1.81</td>
<td>1.81</td>
<td>0.02</td>
</tr>
<tr>
<td>Systemic vasc resistance, dyn·s·cm⁻⁵</td>
<td>7</td>
<td>1,491</td>
<td>475</td>
<td>1,812</td>
<td>732</td>
<td>0.06</td>
</tr>
<tr>
<td>Tau (arterial), s</td>
<td>9</td>
<td>1.40</td>
<td>0.30</td>
<td>1.51</td>
<td>0.39</td>
<td>0.07</td>
</tr>
<tr>
<td>Derived impedance parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zₜ, dyn·s·cm⁻⁵</td>
<td>7</td>
<td>1,491</td>
<td>475</td>
<td>1,812</td>
<td>732</td>
<td>0.06</td>
</tr>
<tr>
<td>Zₜ, dyn·s·cm⁻⁵</td>
<td>7</td>
<td>151</td>
<td>52</td>
<td>164</td>
<td>76</td>
<td>0.72</td>
</tr>
<tr>
<td>Reflection coefficient</td>
<td>7</td>
<td>0.82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse waveform indexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>9</td>
<td>43.2</td>
<td>7.4</td>
<td>41.7</td>
<td>10.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Reflection wave ratio, %</td>
<td>9</td>
<td>178.8</td>
<td>24.4</td>
<td>177.8</td>
<td>39.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Ejection duration, ms</td>
<td>9</td>
<td>330.2</td>
<td>26.8</td>
<td>326.7</td>
<td>22.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Aortic PWV, m/s</td>
<td>7</td>
<td>11.36</td>
<td>3.64</td>
<td>10.99</td>
<td>3.17</td>
<td>0.48</td>
</tr>
<tr>
<td>Brachial PWV, m/s</td>
<td>7</td>
<td>6.12</td>
<td>0.93</td>
<td>6.11</td>
<td>0.81</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Zₜ, terminal impedance; Zₜ, characteristic impedance; PWV, pulse wave velocity. Because of flow catheter movement during study period, complete results were only available for 7/9 subjects (n). Pressure results were available for all subjects.

Fig. 2. Acute effect of sublingual estradiol (E2) on aortic input impedance. There was no effect of estradiol at 10 min or at completion of the study at 20 min. NS, not significant.
**DISCUSSION**

This study found no significant acute effects of estradiol administration on ventricular or arterial function, despite achieving markedly supraphysiological estradiol serum concentrations within the study period. There was a significant decrease in cardiac output and heart rate in the pooled data of all subjects following estrogen administration. This result is surprising because a number of studies have shown that estrogen may act directly as a smooth muscle relaxant, with consequent vasodilating properties (12, 23). At least one previous study, however, has documented a significant combined decrease in heart rate and cardiac output in association with estrogen therapy (22), similar to the current study. Whereas the decrease in heart rate may be partially responsible for the decrease in cardiac output, in the absence of changes in ventricular function, a further possible mechanism is through a decrease in preload due to venodilation. This is suggested by the tendency toward a decrease in right atrial pressure in the eight subjects in whom it was measured.

There have been no prior invasive human studies of the effect of estradiol on load-independent indexes of LV function. Two studies that have suggested a positive inotropic effect of estrogen found increases in peak aortic flow velocities in response to short-term hormone replacement therapy and attributed those changes in aortic velocities to “enhanced inotropism” (26, 28). These studies were noninvasive and did not record corresponding serum estradiol concentrations. Two further noninvasive echocardiographic studies have also found no effect on cardiac function in response to hormone replacement therapy (24, 35), in agreement with the current study.

The current study confirms what has been found in an isolated rat heart study (6). In that study, 17β-estradiol was associated with a negative chronotropic effect in the right atrium without any negative inotropic effect. Of note, however, is the fact that global ventricular function improved with estradiol only if the coronary arteries had been preconstricted with acetylcholine (6). Because the majority of subjects in the current study had normal coronary arteries, it may be expected that no significant effect on global LV function would be found. A study in the isolated rabbit heart found a significant negative inotropic effect only at very high concentrations (>1 μmol/l) (29). Consistent with a calcium blockade mechanism, a similar negative inotropic effect has been shown in an isolated guinea pig myocyte study, again at high in vitro concentrations (10–30 μmol/l) (11). Another study, in the rat heart following gonadectomy, found that estrogen (2 mg/day) tended to improve the cardiac dysfunction associated with gonadectomy (33). Serum estrogen levels were not measured in that study. A frequent problem with all of the in vivo studies in experimental animals is that significantly higher estrogen concentrations are used than are typically seen during hormone replacement therapy (400–600 pM) making direct extrapolation to effects on cardiac function in postmenopausal women difficult. The current study suggests that even at serum concentrations at around five times the standard therapeutic levels, estrogen does not significantly affect cardiac performance in the acute phase.

Preliminary reports have suggested that estrogen may acutely improve arterial compliance (36). In the study by Stefanadis et al. (36), aortic compliance was calculated from invasively measured pressure-diameter relations. Contrary to this, the current study found a tendency to decreased arterial compliance, in both pressure-volume and pressure-flow protocols. This was suggested by a trend toward an increase in effective
arterial elastance, and an increase in the aortic pressure diastolic decay constant (tau) in aortic pressure waveform analysis. There was no trend with respect to Z\text{a}, augmentation index, or pulse wave velocity. One difference with the study by Stefanadis et al. (36) was that measurements were taken for 40 min rather than 20 min in this study. This timing difference may be crucial because in the noninvasive study by Volterrani and colleagues (39), forearm blood flow changes were not apparent at 20 min but became significant at 40 min. The rationale for completing this study within 20 min was based on results that showed that both the negative inotropic effects in isolated myocytes (11) and activation of nitric oxide synthase from endothelial cells (3) occur within 5 min of estrogen exposure. Whereas longer term estrogen has been shown to improve arterial compliance (derived noninvasively) in some studies (30), this is not a universal finding (8, 10).

Possible reasons contributing to the negative results reported here may relate to the effect of radiographic contrast administered during cardiac catheterization. One effect of cardiac catheterization is to gradually deplete intravascular volume due to the diuretic effect of the contrast in fasting patients. This would be expected to increase the peripheral vascular resistance slightly, as was found in this study (with a tendency to increased arterial elastance and a tendency to increased calculated systemic vascular resistance). Any significant sympathetic response associated with volume depletion would tend to increase heart rate. This was not evident in this study, suggesting that the decrease in heart rate may be a direct effect of estrogen. This is consistent with other data demonstrating a negative chronotropic effect of estrogen (1, 22).

Because different classes of calcium antagonists have been shown to have variable effects on the periphery and on the heart (4), it is conceivable that estrogen may also exhibit selectivity of action. Because the urogenital bed may be considered the prime target for estrogen, regional increases in blood flow may have occurred that were not reflected in overall cardiac output or hemodynamic parameters (23). A number of vascular studies of the effects of estrogen have used intra-arterial injections, making vascular effects more apparent. Nonetheless in the study by Gilligan et al. (7), estradiol doses were used to achieve “premenopausal” estrogen levels. At that concentration, however, estradiol did not directly cause vasodilatation or increase blood flow but only potentiated acetylcholine responses (7). The negative chronotropic effect in the absence of significant vasodilatation remains consistent with calcium antagonism as a possible mechanism of action. Importantly, because this was an acute study, it remains possible that genomic effects of estrogen on other elements in the vascular tree or the heart may be seen with more prolonged use. This may be an important factor in the increase in arterial compliance associated with pregnancy (27).

The absence of any demonstrable benefit of acute estrogen administration in this study may relate to patients continuing their antianginal therapy at the time of catheterization. Previous (32) studies that have found an increase in exercise capacity in patients with angina due to sublingual estrogen administration have studied patients off anginal therapy, which may make any vasodilation easier to detect. Whereas none of the women in this study were taking hormone replacement therapy, a number of the women were already taking long-acting vasodilators, including calcium antagonists, angiotensin-converting enzyme inhibitors, and long-acting nitrates. A recent study (38) has suggested that estrogen may modulate the effect of nitrovasodilators. In that study, whereas higher doses of estrogen (10 \text{\mu M}) were associated with in vitro vasodilatation, no relaxation was seen at 1 nM. In the presence of other vasodilators, including sodium nitroprusside, however, 1 nM estradiol enhanced vasodilation. This study may have been confounded, therefore, by concurrent anginal therapy. Nonetheless, the important conclusion can be made that acute supraphysiological levels of estradiol did not have any additive beneficial hemodynamic effect for women already receiving appropriate cardiovascular treatment. A subanalysis of subjects who were not taking vasodilators (9 of the 18 women studied) did not appreciably alter the cardiac output results. There remained a trend toward a decrease in cardiac output from $4.7 \pm 0.9$ to $4.2 \pm 1.1$ l/min ($n = 6$ subjects, $P = 0.08$). Heart rate changes following estrogen in women not taking vasoactive therapy remained significant, decreasing from $74.4 \pm 9.7$ to $71.4 \pm 10.1$ ($n = 9$ subjects, $P = 0.03$).

The kinetics of sublingual estradiol were not examined in this study. Our concern was to ensure that sufficient serum drug levels were achieved within the time frame of the study. The dose was chosen because it had previously been shown to acutely increase serum levels in a cohort of postmenopausal women (32). The levels achieved in the current study are similar to those from the study by Rosano et al. (32) ($2,531 \pm 1,192$ pmol/L), despite the fact that the estradiol was given 40 min before exercise in that study. This suggests that the serum level increase quickly and remain elevated in the short term. A pharmacodynamic study in five women suggested that the peak level occurred within 2 h and had returned to baseline before 24 h (2).

In conclusion, despite increasing serum estradiol from low postmenopausal to supraphysiological levels, we found no acute alteration in either ventricular or vascular function. There was a small but significant decrease in heart rate associated with a significant decrease in cardiac output over the entire cohort without any evidence of a negative inotropic effect. Previously described improvements in arterial compliance due to estrogen may be related to structural or receptor-mediated changes associated with longer exposure.

The assistance of the staff of the St. Vincent’s Hospital Cardiac Catheterisation Laboratory is gratefully acknowledged.

This work was supported by a Postgraduate Research Fellowship for C. Hayward and a Project Grant for R. P. Kelly, both from the National Health and Medical Research Council (Canberra, Australia). C. Hayward is currently supported by an Overseas Research
Fellowship from the National Heart Foundation (Canberra, Australia).

REFERENCES


