BASIC SCIENCE

17-Beta-Estradiol Increases Cardiac Remodeling and Mortality in Mice With Myocardial Infarction

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OBJECTIVES This study was designed to examine the effects of estrogen replacement on infarct size, ventricular remodeling, and mortality after myocardial infarction (MI) in mice.

BACKGROUND Observational and clinical studies suggest that the cardiovascular effects of hormone replacement therapy can differ depending on the patient population studied. No prospective studies have examined the effect of estrogen on outcomes following MI. We now examine the effects of estrogen replacement on infarct size, ventricular remodeling, and mortality after MI in mice.

METHODS Myocardial infarction was induced by left coronary artery ligation in ovariectomized female mice treated with 17-beta-estradiol (E2) or placebo. At either one day or six weeks after MI, hemodynamic function was assessed, animals were euthanized, and infarct size was determined.

RESULTS 17-Beta-estradiol–treated mice had smaller infarcts than placebo-treated animals both one day (18% decrease; p < 0.01), and six weeks (14% decrease; p < 0.05) following MI. E2 reduced cardiomyocyte apoptosis as assessed by the terminal deoxynucleotidyl transferase uridine nucleotide end-labeling method (50% reduction, p < 0.05) and caspase 3 activation (33% reduction, p < 0.05). Despite having smaller infarcts, however, left ventricular mass increased more in the E2-treated animals (16% greater; p < 0.01). Left ventricular weight was positively correlated with infarct size in the estrogen-treated animals (R^2 = 0.79, p = 0.0001). 17-Beta-estradiol treatment also significantly increased mortality in the infarcted animals (relative risk of death = 2.4; 95% confidence interval 1.2 to 5.3).

CONCLUSIONS Estrogen replacement therapy reduces infarct size and cardiomyocyte apoptosis in mice. However, estrogen increased post-MI ventricular remodeling and mortality. Further studies will be necessary to elucidate the mechanisms underlying the complex effects of estrogen observed in the present study. (J Am Coll Cardiol 2003;41:2084–92) © 2003 by the American College of Cardiology Foundation

Many observational studies suggest that estrogen replacement therapy has cardioprotective effects in postmenopausal women (1,2). However, recent clinical trials have failed to show a cardiovascular benefit of hormone replacement therapy (HRT) in women with established coronary artery disease (reviewed in [3]). These findings suggest that the effects of HRT may differ in different populations of women. (4).

Numerous animal studies have demonstrated beneficial effects of estrogen on the vascular system (reviewed in [5–8]). For example, it has been shown that estrogen inhibits vascular remodeling in response to mechanical injury (9–16) and with hyperlipidemia (17,18). Less is known, however, regarding the effects of estrogen on the heart. Cardiomyocytes express both known estrogen receptors (ER)-alpha and ER-beta (19,20), and estrogen has recently been shown to attenuate the development of cardiac hypertrophy in response to pressure overload (21). Studies of the effects of estrogen on cardiac ischemia and myocardial infarction (MI) have revealed conflicting results (22–29). To date, no studies have examined the effects of estrogen on acute infarct size or on long-term remodeling and survival post-MI. In the current study, we examined the effects of estrogen replacement on infarct size, mortality, and cardiac remodeling after MI in ovariectomized female mice. We now demonstrate that estrogen reduces infarct size but increases left ventricular (LV) remodeling and death following MI.

METHODS

Study plan. The study protocols are shown schematically in Figure 1. On day −14, ovariectomized mice were treated with placebo or 17-beta-estradiol (E2)-containing pellets (0.36 mg E2/90-day release pellet; Innovative Research of...
America, Sarasota, Florida). One week later, baseline echocardiographic studies were performed (day 7). On day 0, MI was induced by ligation of the left coronary artery. In the long-term study, 126 mice randomized to placebo or E2 treatment were subjected to MI or a sham operation, resulting in the following four groups: placebo-sham (n = 22), E2-sham (n = 22), placebo-MI (n = 40), and E2-MI (n = 42). Echocardiography was performed five weeks post-MI. At six weeks, mice underwent invasive hemodynamic evaluation and were euthanized by intravenous injection of 1 M KCl solution while under general anesthesia. Hearts were harvested for determination of organ weights and infarct size. One animal in each of the E2-sham, placebo-MI, and E2-MI groups was excluded because of postoperative infection. In the short-term study, 36 animals randomized to placebo (n = 18) or E2 treatment (n = 18) were euthanized 24 h after MI.

Animals. Female C57BL/6J mice (Taconic, Germantown, New York) 8 to 10 weeks of age were studied. Mice were housed in an AAALAC-approved animal facility with 12-h light/dark cycles and given free access to standard rodent chow (PROLAB, Syracuse, New York) and water. The protocols were approved by the Institutional Animal Care and Use Committee.

Surgical procedures. Anesthesia was induced by inhalation of isoflurane (2.0% to 2.5% vol/vol), which was supplemented by intraperitoneal injection of ketamine (45 mg/kg body weight [BW]) during MI induction. Body temperature was maintained at 37 ± 0.2°C using a closed-loop system (Barnant Company, Barrington, Illinois). Ovariectomies and pellet implantations were performed as described (13–16,21). Myocardial infarctions were induced as described previously (30). Briefly, mice were mechanically ventilated and MI was induced by ligating the left coronary artery 1 mm below the left atrial appendage. Sham-operated animals underwent a thoracotomy, but no suture was placed in the myocardium.

Long-Term Study

For the invasive and noninvasive hemodynamic measurements the body temperature was maintained at 37 ± 0.2°C.

Echocardiography. Transthoracic echocardiography was performed using an HDI 5000 machine (ATL Inc., Bothell, Washington) and a 10 MHz linear array transducer as described (30). M-mode tracings and two-dimensional images were recorded from the short-axis view. Left ventricular end-diastolic and end-systolic diameters and heart rate were measured averaging values obtained from three cardiac cycles. Ventricular dimensions were normalized to body weight. Fractional shortening was calculated using a standard equation (30).

Invasive hemodynamic analyses. Hemodynamic measurements were performed at week 6 but were technically not feasible in two, four, zero, and two animals in the placebo-sham, E2-sham, placebo-MI, and E2-MI groups, respectively. A 1.4 F Millar transducer (Millar Instruments, Inc., Houston, Texas), connected to a computerized data acquisition system (Powerlab, ADInstruments, Grand Junction, Colorado), was introduced into the right common carotid artery. The Chart 4 data analysis software (ADInstruments) was used to calculate the first derivative of LV pressure (dp/dt). Left ventricular end-diastolic pressures were measured by averaging three manual measurements of three cardiac cycles each as described previously (30).

Tissue harvest. After the invasive hemodynamic studies, 0.5 ml of blood was obtained and the heart and uterus were excised. Atria, great vessels, and the right ventricular free wall were separated from the LV and weighed. The left ventricles were embedded in paraffin and 4-μm-thick sections were stained with Gomori trichrome (21).

Determination of chronic infarct size (six weeks). Infarct size in the long-term study was measured by compressing the LV between two glass slides and capturing images of both sides using a computerized image analysis system (Image-Pro Plus, Image Processing Solutions, Inc., North Reading, Massachusetts). The infarct area was distinguishable from noninfarcted myocardium by the white color of the fibrous infarct. Infarct size was determined by calculating the relative surface area of the infarct as a percentage of the total LV surface area. Animals with infarcts ≤15% were

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**Abbreviations and Acronyms**

- **BW** = body weight
- **E2** = 17-beta-estradiol
- **ER** = estrogen receptor
- **FL** = femur length
- **HRT** = hormone replacement therapy
- **LV** = left ventricle
- **LVW** = left ventricular weight
- **MI** = myocardial infarction
- **TUNEL** = transferase uridine nucleotide end-labeling method

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Figure 1. Study plan. Animals were ovariectomized (Ovex) 21 days before myocardial infarction (MI), with initiation of placebo or estrogen treatment at day −14 (P/E2), and baseline echocardiographic studies (Echo) performed on day −7 and day 35. Animals were harvested one day after MI for the short-term study (upper panel) and six weeks after MI for the long-term study (lower panel).
excluded from further analyses (n/H11005 = 9 placebo-MI vs. n/H11005 = 6 E2-MI; p/H11005 = ns). All of the data analyses were also performed with these small-infarct mice included, and in no case were the results altered by inclusion of these mice (data not shown).

Myocyte cross-sectional area measurements. Myocyte cross-sectional area was measured from the formalin-fixed sections. Myocytes distant from the infarct zone, sectioned transversely at the level of the nucleus, were analyzed. Only myocytes that appeared nearly round were chosen for measurement. The image analysis system was calibrated and individual myocytes areas were traced and quantified; 110 to 150 myocytes were measured per heart.

Short-Term Study

Determination of acute infarct size (day +1). The left ventricle was sliced into 0.75-mm-thick sections. Each section was weighed and stained in a 1% triphenyltetrazolium chloride solution in phosphate-buffered saline (pH 7.4) for 30 min at 37°C (31). The slices were placed between two glass slides and images of both sides were digitally captured. The relative area of the infarct was determined by planimetry. The average infarct cross-sectional area of the two sides of each section was then multiplied by the weight of the section to calculate the amount of infarct tissue in mg for each section. These values were then summed and infarct size was expressed in absolute mg of infarcted tissue and as relative weight to LV weight as described previously (31).

Terminal deoxynucleotidyl transferase uridine end-labeling (TUNEL). Formalin-fixed, paraffin-embedded myocardial sections were deparaffinized and rehydrated. Samples were treated with Proteinase K (Sigma) for 30 min and incubated with terminal deoxynucleotidyl transferase in reaction buffer containing digoxigenin-labeled uridine triphosphate for 60 min at 37°C, followed by FITC-tagged, anti-digoxigenin antibody (Intergen). Sections were counterstained with a mouse monoclonal anti-sarcomeric alpha-actinin antibody (Sigma) and stained with a rhodamine red-labeled donkey anti-mouse secondary antibody. Positive controls were treated with DNAse I. Negative controls were incubated in reaction buffer not containing terminal deoxynucleotidyl transferase. Nuclei were stained with 4',6-diamidino-2-phenylindole and 1,200 to 1,600 nuclei were counted in each zone (infarct and peri-infarct).

Caspase 3 activity assay. Snap-frozen myocardial tissue was pulverized in a mortar and pestle cooled with liquid nitrogen. Approximately 20 mg of powdered tissue was vortexed in ice-cold lysis buffer containing 50 mM Pipes/KOH (pH 6.5), 2 mM EDTA, 0.1% chaps, 5 mM DTT, 20 μg/ml leupeptin, 10 μg/ml pepstatin A, 10 μg/ml aprotinin and incubated on ice for 30 min. The samples were cleared by centrifugation and protein concentration measured. Next, the fluorometric caspase substrate, N-acetyl-Asp-Glu-Val-Asp-7-amido-4-trifluoromethylcoumarin (Ac-DEVD-AFC) was added and incubated for 1 h at 37°C. Selected samples were run with the corresponding caspase inhibitor, DEVD-CHO. Cleavage of the fluorometric substrate was quantified by measuring its emission at 405 nm with a plate reader.

Table 1. Animal Characteristics

<table>
<thead>
<tr>
<th>Animal Characteristic</th>
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<th>E2</th>
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<tr>
<td>BWMI [g]</td>
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<td>21.9 ± 0.3</td>
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<td>25.7 ± 0.6</td>
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<td>BWchange [g]</td>
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<td>1.9 ± 0.3*</td>
<td>4.1 ± 0.4</td>
<td>0.9 ± 0.04*</td>
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<tr>
<td>FL [mm]</td>
<td>15.07 ± 0.14</td>
<td>14.84 ± 0.13</td>
<td>15.06 ± 0.08</td>
<td>14.73 ± 0.05</td>
</tr>
<tr>
<td>Uterus [mg]</td>
<td>8 ± 1</td>
<td>189 ± 14*</td>
<td>8 ± 1</td>
<td>192 ± 12*</td>
</tr>
</tbody>
</table>

Body weight (BW) at time of myocardial infarction (MI), harvest (Har) and weight change (change), femur length (FL), and uterine weight. All values as mean ± SEM. P ≤ 0.05 E2-sham vs. placebo-sham and E2-MI vs. placebo-MI.

E2 = 17-beta-estradiol.

Figure 2. Kaplan-Meier survival curve. The mortality in the E2-MI animals was significantly greater than in the Placebo-MI animals p < 0.02. *P ≤ 0.05 E2-MI vs. E2-sham, †P ≤ 0.05 E2-MI vs. placebo-MI. Abbreviations as in Figure 1.
505 nm with excitation at 400 nm using a SpectroFluorimeter (Beckman). Standard curves were created using the fluorometric substrate (AFC) at concentrations ranging from 1 to 16 μM. Caspase 3 activity was expressed as the amount of AFC cleaved per hour per mg of protein (μM/h/mg).

Both TUNEL staining and caspase three assays were performed on a subset of infarcted hearts that were matched for infarct size in the E2-treated and placebo-treated animals (n = 6 for each group).

Data analysis and statistics. All data collection and analysis was performed by observers blinded to treatment. Values are expressed as mean ± SEM. Comparison of the Kaplan-Meier survival curves was performed using a log-rank test. The comparison of the two groups in the short-term study was performed using an unpaired Student t test. For multiple-group comparisons, one-way analysis of variance was used, followed by Student-Newman-Keuls post hoc pairwise testing. Values of p ≤ 0.05 were considered statistically significant.

RESULTS

Ovariectomized animals had undetectable E2 serum levels (<5 pg/ml), and these were restored to physiologic levels (81 ± 13 pg/ml) by E2 replacement. The placebo-treated animals also had an atrophied uterus (≤10 mg) that was reversed by E2 treatment (Table 1).

Long-Term Study

To examine the long-term effects of estrogen on LV remodeling and survival, mice were randomized to either E2 or placebo, underwent MI or sham operation, and then were followed for six weeks after surgery.

Mortality. In the sham-operated animals, four animals died in each treatment group (p = ns; Fig. 2). Mortality in the placebo-MI animals was 29% (p = ns vs. both sham groups). In contrast, mortality in the infarcted, E2-treated group was 60% (p < 0.02 vs. placebo-MI; Fig. 2). In the infarcted animals, E2 treatment was associated with a risk ratio for death of 2.4 (95% confidence interval 1.2 to 5.3).
Infarct size. The mean infarct size assessed six weeks after infarction was significantly smaller in the E2-MI group (24 ± 1%) compared with the placebo-MI group (28 ± 1%; \( p \leq 0.05 \); Fig. 3).

Assessment of LV Remodeling Post-MI

Echocardiography. At baseline, there were no significant differences in the echocardiographic measurements of cardiac structure or function between the E2-treated and the placebo-treated animals (Fig. 4). Induction of MI resulted in increased end-systolic and end-diastolic diameters (Fig. 4). The infarcted mice also demonstrated significantly reduced cardiac function with decreased fractional shortening (Fig. 4). 17-Beta-estradiol–treated animals developed larger end-systolic and end-diastolic diameters than the placebo-treated mice. 17-Beta-estradiol treatment had no effect, however, on MI-induced decreases in fractional shortening (Fig. 4). No echocardiographic parameters changed significantly over time in the sham group.

Invasive hemodynamics. In the sham group, E2 treatment decreased positive dp/dt by 13% (\( p \leq 0.05 \)) and increased negative LV dp/dt by 12% (\( p \leq 0.05 \)) compared to

<table>
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<tr>
<th></th>
<th>Sham Placebo</th>
<th>E2</th>
<th>MI Placebo</th>
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<td>n</td>
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<td>13</td>
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<tr>
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<td>8 ± 1</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
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<td>Pos dp/dt [mm Hg s(^{-1})]</td>
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<td>9,424 ± 351†</td>
<td>8,184 ± 404*</td>
<td>7,804 ± 384*</td>
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<tr>
<td>Neg dp/dt [mm Hg s(^{-1})]</td>
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<td>−9,103 ± 348†</td>
<td>−7,465 ± 441*</td>
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<td>558 ± 8</td>
<td>563 ± 9</td>
<td>560 ± 11</td>
<td>573 ± 8</td>
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</tbody>
</table>

Systolic, mean, and diastolic aortic pressure (SAP, MAP, DAP), left ventricular systolic and end-diastolic pressure (LVSP, LVEDP), positive (Pos) and negative (Neg) dp/dt, and heart rate (HR). All values as mean ± SEM. \( *p \leq 0.05 \) placebo-MI vs. placebo-sham and E2-MI vs. E2-sham; \( †p \leq 0.05 \) E2-sham vs. placebo-sham.

E2 = 17-beta-estradiol; MI = myocardial infarction.

Figure 5. (Left panels) Infarct-induced increases in left ventricular (LV) weight indexed to body weight (BW) (upper panels) or femur length (FL) (lower panels) were exacerbated by estrogen treatment. (Right panels) Regression analysis revealed greater left ventricular remodeling with increasing infarct size in E2-treated animals compared with placebo-treated animals. The femur length was only obtained in a subgroup of animals (8 E2-MI and 9 placebo-MI animals). \( *p \leq 0.05 \) placebo-MI vs. placebo-sham and E2-MI vs. E2-sham; \( †p \leq 0.05 \) E2-MI vs. placebo-MI. Abbreviations as in Figure 1.
placebo-shams (Table 2). Myocardial infarction significantly decreased positive LV $\frac{dp}{dt}$ (placebo-MI: $-25\%$, $p \leq 0.001$ vs. placebo-sham; E2-MI: $-18\%$, $p \leq 0.05$ vs. E2-sham) and increased negative LV $\frac{dp}{dt}$ (placebo-MI: $28\%$, $p \leq 0.001$ vs. placebo-sham; E2-MI: $22\%$, $p \leq 0.01$ vs. E2-sham; Table 2). 17-Beta-estradiol treatment had no effect on MI-induced changes in LV $\frac{dp}{dt}$. The decrease in systolic function following MI was accompanied by a trend toward decreased LV systolic pressure that was not significant ($p = 0.09$; Table 2). No differences in LV end-diastolic pressure, aortic pressure, or heart rate were observed between the groups (Table 2).

**Left ventricular weight.** Left ventricular weight (LVW) was indexed to BW and femur length (FL). E2 had no effect on LVW in the sham-operated animals. Myocardial infarction caused significant increases in LV mass, and the MI-induced increase in LV mass was greater with E2 treatment. LVW/BW increased 31% in the E2-treated mice, as compared with 26% in placebo-treated mice ($p < 0.01$; Fig. 5). Similarly, LVW/FL increased 28% in the E2-MI mice, compared with only 24% in the placebo-MI mice ($p < 0.01$; Fig. 5).

To determine whether E2 treatment altered the relationship between LVW and infarct size, linear regression analysis was performed. In the placebo-MI mice, even large infarcts were associated with only a small increase in LV mass. In contrast, in the E2-MI mice, larger infarcts resulted in a significantly larger increase in LV mass (LVW/BW: $r = 0.79$, $p \leq 0.0001$; LVW/FL: $r = 0.92$, $p \leq 0.0002$; Fig. 5).

To determine whether the greater increase in LV mass in the E2-MI mice resulted from increased myocyte size, myocyte cross-sectional area was measured morphometrically. In the placebo-treated mice, MI caused a modest rise in myocyte cross-sectional area that did not reach statistical significance (Fig. 6). In contrast, in the E2-treated animals, MI caused a significant increase in myocyte CSA (Fig. 6; $p < 0.05$). In addition, as with LV mass, myocyte CSA correlated strongly with infarct size ($r = 0.71$, data not shown) in the E2-MI mice but not in the placebo-MI group.

**Short-Term Study**

One potential explanation for the apparently smaller infarcts observed in the estrogen-treated mice in the long-term study is that mice with larger infarcts in this group may have died. To explore further whether E2 reduces infarct size, an additional 36 mice were studied. At 24 h after coronary ligation, placebo-treated mice had a mean infarct size of $23.7 \pm 0.9$ mg, whereas mean infarct size in the E2-treated mice was significantly smaller ($19.4 \pm 0.9$ mg; $p < 0.01$; Fig. 7). Infarct size expressed as a relative proportion of total LV mass was also less in the E2-MI group (data not shown).

To determine whether estrogen treatment altered infarct-induced cardiomyocyte apoptosis, TUNEL stains and caspase 3 assays were performed on myocardial sections from a subset of infarcted hearts in the short-term study. Hearts from E2-treated mice demonstrated fewer TUNEL-positive nuclei compared with placebo-treated mice in the infarct zone ($8.7 \pm 1.4\%$ vs. $17.7 \pm 4.1\%$, respectively, $p = 0.065$) and in the peri-infarct zone ($8.4 \pm 0.8\%$ vs. $15.9 \pm 3.0\%$, respectively, $p < 0.05$; Figs. 8A and 8B). Consistent
Figure 8. (A) Examples of transferase uridine nucleotide end-labeling method (TUNEL) staining of the peri-infarct zone in myocardial sections from placebo and 17-beta-estradiol (E2)–treated mice 24 h following coronary ligation. TUNEL–positive nuclei are green. Arrows indicate examples of TUNEL–positive cardiomyocyte nuclei. (B) Quantification of TUNEL–positive nuclei expressed as percent total nuclei on a given section. Infarct zone is shown on the left and peri-infarct zone on the right. (C) Caspase 3 activity measured within the infarct zone 24 h following coronary ligation. *p = 0.065, E2 vs. placebo. †p < 0.05, E2 vs. placebo.
with the TUNEL staining, caspase 3 activation was diminished in the infarct zone from the E2-treated mice compared with the placebo-treated mice (3.85 ± 0.58 vs. 5.98 ± 0.62 μM/h/mg, p < 0.05; Fig. 8C).

DISCUSSION

In the present study, we examined the effects of E2 replacement on MI in ovariectomized female mice. Though previous studies have suggested that E2 treatment reduces ischemia/reperfusion injury (22–26), experiments analyzing the effect of E2 treatment on infarct size have revealed conflicting results (28,29). In the current study, we found that E2 treatment slightly decreased infarct size in mice at both 24 h and six weeks after MI, but despite this effect, the estrogen–treated animals developed more LV remodeling and suffered significantly greater mortality. The most likely explanation for the differences between our findings and previous reports is that our study included a larger population of animals, which enhanced its statistical power. Species differences or different methods of hormone administration could also have contributed.

There are several potential mechanistic explanations for the small reduction in infarct size observed in the E2-treated mice. In vitro, estrogen inhibits apoptosis in cultured cardiomyocytes (32), and to the extent that apoptosis participates in infarct-induced cell death (33), this represents a potential mechanism by which infarct size may be reduced by E2 treatment. Our current results showed that E2 significantly decreased two measures of apoptosis, providing one potential mechanism by which E2 reduces infarct size. Although the molecular signaling pathways underlying the pro–survival effect of E2 on cardiomyocytes are unknown, ongoing studies in our lab are exploring this important observation further.

Surprisingly, despite a reduction in infarct size, E2 increased ventricular remodeling over the six-week follow-up period, and this was associated with a more than twofold increase in mortality. We also observed that E2 significantly increased LVW for a given infarct size, and this was at least in part related to greater myocyte hypertrophy. These findings are of potential clinical relevance, as cardiac hypertrophy and remodeling are important negative predictors of morbidity and mortality in patients with heart failure (34).

The current finding that E2 accentuates post-MI remodeling is in contrast to the effects of E2 in pressure overload, where E2 treatment exerts antihypertrophic effects (21,35,36). This supports the notion that there are substantial differences in the effects of E2 on ventricular remodeling that depend at least in part on the stimulus for myocyte hypertrophy (such as post–MI remodeling vs. pressure overload hypertrophy). It is interesting to speculate on the possibility that estrogen–mediated enhanced activation of signaling pathways known to exert anti-apoptotic effects (such as Akt) may also phosphorylate downstream signaling proteins (such as GSK-3-beta) that have previously been shown to regulate cardiac hypertrophy. Further molecular studies will be required to elucidate the mechanisms by which estrogen augmented cardiac hypertrophy in the current model.

Though it might be expected that we would observe an increase in mortality in the estrogen–treated mice because of their greater degree of LV remodeling, the mechanism(s) that mediate this effect also remain unclear. Despite twice-daily observation, the animals died without overt signs of heart failure. An increased risk of sudden death could have occurred, related either to infarct- or hypertrophy-associated increases in electrical inhomogeneity. E2–induced alterations in circulating neurohumoral factors also could contribute to an increase in sudden death. Estrogen–induced increases in thrombosis could also be hypothesized to explain the increased mortality, perhaps because of an increased risk of thromboembolism, though again no specific evidence has been observed to support this.

In addition to the lack of mechanistic insight provided by the current studies, additional limitations also deserve mention. A number of additional clinically relevant protocols would be of interest to explore. For example, what would be the effect of E2 treatment if initiated in stable mice that have survived an MI? Similarly, would discontinuation of E2 treatment at the time of the infarct alter the observed effects of estrogen treatment? Are there other medical interventions such as beta-blockers or angiotensin-converting enzyme inhibitors that might alter the effects of estrogen? These clinically relevant studies are currently ongoing in our laboratory.

In conclusion, the current studies demonstrate that estrogen treatment slightly reduces infarct size in mice, but despite this protective effect, estrogen also increases LV remodeling and post-infarct mortality. Though further study will be required to elucidate the mechanisms responsible for these effects, our findings highlight the complexity of the cardiovascular effects of estrogen, and as such demonstrate the importance of both protective and harmful cardiovascular effects of this hormone.

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van Eickels et al.  
Estrogen and Myocardial Infarction in Mice


