Methylation of 2-Hydroxyestradiol in Isolated Organs

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Abstract—Vascular smooth muscle and glomerular mesangial cells in culture express a biochemical pathway that methylates 2-hydroxyestradiol (17β-estradiol metabolite) to produce 2-methoxyestradiol, a cell growth inhibitor that may mediate the cardiorenal protective effects of 17β-estradiol. Whether this pathway exists in intact organ systems is currently unclear. Accordingly, the purpose of the present investigation was to characterize the methylation of 2-hydroxyestradiol in intact organs from both male and female rats. No significant differences were detected in the ability of male and female tissues to methylate 2-hydroxyestradiol. In isolated hearts, kidneys, and mesenteries perfused with Tyrode’s solution, Km values for 2-hydroxyestradiol methylation were 0.175 ± 0.021, 0.387 ± 0.054, and 0.495 ± 0.089 μmol/L, respectively, and Vmax values were 21.0 ± 1.58, 24.9 ± 1.49, and 1.01 ± 0.148 pmol 2-methoxyestradiol · min⁻¹ · ml⁻¹ per gram, respectively. The catalytic efficiency (Vmax/Km) was greatest in the heart compared with the kidney and mesentery (132 ± 14.3, 78.4 ± 15.1, and 2.30 ± 0.263 pmol 2-methoxyestradiol · min⁻¹ · ml⁻¹ · μmol/L⁻¹ per gram, respectively). In the kidney, the catechol-O-methyltransferase inhibitor quercetin and norepinephrine (10 μmol/L) reduced methylation of 2-hydroxyestradiol by approximately 90% and 41%, respectively. Importantly, methylation in the kidney was inhibited by an average of 16.6 ± 1.80% by endogenous norepinephrine released by renal artery nerve stimulation. Our results indicate that a robust 2-hydroxyestradiol methylation pathway exists in the kidney and heart, but not in the mesentery, and that this pathway is mediated by catechol-O-methyltransferase. Our findings also suggest that catecholamines may interfere with 2-hydroxyestradiol methylation and thereby attenuate the cardiorenal protective effects of 17β-estradiol. (Hypertension. 2003;42:82-87.)

Key Words: vascular diseases ■ coronary artery disease ■ sympathetic nervous system ■ renal disease ■ catecholamines

Blood vessels are protected from disease by 17β-estradiol,1–3 but by not conjugated equine estrogens.4–5 Apparently, the vascular protective effects of 17β-estradiol are mediated in part via the antiproliferative effects of 17β-estradiol on vascular smooth muscle cells.2,3

Our findings support the concept that the antiproliferative effects of 17β-estradiol on vascular smooth muscle cells are not mediated by estrogen receptors, but rather are due to the direct effects of metabolites of 17β-estradiol on molecular processes regulating cell proliferation.6–9 In this regard, in vascular smooth muscle cells, 17β-estradiol is converted to 2-hydroxyestradiol (2OHE) by cytochrome P450s, and 2OHE is methylated by catechol-O-methyltransferase (COMT) to form 2-methoxyestradiol (2MeOE). The order of potency for inhibition of vascular smooth muscle cell growth is 2MeOE > 2OHE > 17β-estradiol, whereas the order of potency at estrogen receptors is 17β-estradiol > 2OHE > 2MeOE (essential inactive). Moreover, blockade of cytochrome P450s inhibits the antiproliferative effects of 17β-estradiol, but not 2OHE or 2MeOE, and blockade of COMT inhibits the antiproliferative effects of both 17β-estradiol and 2OHE, but not 2MeOE. These findings support the conclusion that the 2OHE methylation pathway plays a key role in determining the vascular protective effects of 17β-estradiol and 2OHE.

Catecholamines are physiological substrates of COMT10 and therefore may inhibit the 2OHE methylation pathway. In support of this hypothesis, increased synthesis of catecholamines under pathological conditions increases the risk of vaso-occlusive and renal disorders.11

Considering the importance of the 2OHE methylation pathway as indicated by our in vitro studies, the objectives of this study were to (1) determine whether this metabolic pathway exists in intact and physiologically relevant vascular beds, specifically, the perfused kidney, heart (coronary circulation), and mesentery; (2) determine and compare the kinetic parameters for the 2OHE methylation pathway in these organs; and (3) examine whether exogenous and endogenous catecholamines block this pathway in the intact kidney.

Materials and Methods

Animals

Male and female Sprague-Dawley rats (n=5 for each group) obtained from Charles River (Wilmington, Mass) were housed at the...
Organ Perfusion
All organs were prepared and perfused at a rate of 5 mL/min and equilibrated for 40 minutes with Tyrode’s solution, followed by 20 minutes with Tyrode’s solution containing 0.57 mmol/L ascorbic acid. Ascorbic acid was essential to prevent oxidation of the substrate 2OHE.12

Preparation of Kidneys for Perfusion
Rat kidneys from male and female rats were prepared for perfusion as previously described.13

Preparation of Hearts for Perfusion
Rat hearts from male and female rats were perfused using the Langen-dorff method. The thoracic cavity was opened, and the heart was excised and immediately placed in cold Tyrode’s solution (4°C). A polyethylene-240 tube was placed in the aorta while the heart was in the cold solution. The tube was secured in place, and the heart was connected to a perfusion pump. A second polyethylene-240 tube was placed in the left ventricle and secured in place to ensure that only perfusate from the coronary circulation was collected.

Preparation of Mesenteries for Perfusion
Rat superior mesenteric vascular beds from male and female rats were prepared for perfusion as previously described.14

Concentration-Dependent Metabolism of 2OHE
Organs were perfused with 0.3 to 10 μmol/L 2OHE in the presence and absence of 10 μmol/L quercetin (a COMT inhibitor) as appropriate. Kinetic parameters were calculated using GraphPad Prism 3.0.

Inhibition of 2OHE Methylation by Exogenous Catecholamines
Kidneys were perfused with Tyrode’s solution containing 2OHE (0.3 μmol/L for male, 0.05 μmol/L for female) and 0.57 mmol/L ascorbic. Male kidneys were perfused in the presence and absence of 10 to 100 μmol/L norepinephrine or epinephrine, and female kidneys were perfused in the presence and absence of 0.5 μmol/L epinephrine. The perfusate was collected and analyzed.

Inhibition of 2OHE Methylation by Endogenous Catecholamines
An electrode was placed around the renal artery, and stimulation was initiated at 7 Hz for a few seconds to ensure that the renal sympathetic nerves were active. Activity was determined by measuring the change in perfusion pressure using a polygraph. The kidney was perfused with Tyrode’s solution containing 2OHE (0.1 μmol/L), a re-uptake inhibitor, desipramine (10 μmol/L), and a monoamine oxidase inhibitor, pargyline (500 μmol/L), to allow norepinephrine to diffuse in the kidney. Perfusate samples were then collected in unstimulated kidneys (control) or kidneys stimulated at 12 Hz for 8 minutes.

Sample Preparation and High-Performance Liquid Chromatography Analysis
Internal standard was added (16α-hydroxyestradiol) to each sample before processing. Samples were applied to a Waters™ Sep-Pak® column (reverse phase; C18), and the column was washed with 5 mL of 20% methanol. 2MeOE was eluted with 2 mL of 100% methanol. The eluted samples were further concentrated under vacuum, and the samples were extracted in methylene chloride 3 times. Samples were dried under vacuum and redissolved in water and methanol, and 2MeOE was quantified as previously described.7

Statistics
All experiments were conducted with at least 5 subjects. Results are presented as mean±SEM. Statistical analyses were performed using ANOVA, paired Student’s t test, or Fisher least significant difference test, as appropriate. A value of P<0.05 was considered statistically significant.

Results
In both male and female rats, 2OHE, in a rapid transit pass through the coronary and renal circulation, was methylated in a concentration-dependent manner (0.1 to 3 μmol/L) (Figure 1). Concentrations of 2OHE as low as 0.1 μmol/L were methylated in measurable amounts during a rapid pass through the kidney and heart. In male and female kidneys, a concentration of 0.1 μmol/L 2OHE produced an average of 0.881±0.052 and 1.12±0.236 nmol 2MeOE/5 min, respectively, and in male and female hearts, an average of 1.07±0.070 and 0.857±0.138 nmol 2MeOE/5 min, respectively. At a concentration of 3 μmol/L 2OHE, in male and female kidneys, this amount increased to a maximum of 4.48±0.240 and 4.26±0.783 nmol 2MeOE/5 min, respectively, and in male and female hearts, this amount increased to a maximum of 2.69±0.190 and 2.82±0.167 nmol 2MeOE/5 min, respectively.

The concentration-response data were employed to calculate the kinetic parameters for the methylation of 2OHE (Figure 2). In the male heart, the apparent Ka for 2OHE was 0.148±0.018 μmol/L versus 0.215±0.038 μmol/L in the female heart (not significant). In the male heart, the Vmax was 19.2±1.73 pmol 2MeOE·min⁻¹·mL⁻¹ per gram versus 23.8±2.62 pmol 2MeOE·min⁻¹·mL⁻¹ per gram in the female heart (not significant). In the male heart, the Vmax/Km was 137±15.3 pmol 2MeOE·min⁻¹·mL⁻¹·μmol⁻1/L per gram versus 126±30 pmol 2MeOE·min⁻¹·mL⁻¹·μmol⁻1/L per gram in the female heart (not significant).

In the male kidney, the Km was 0.407±0.028 μmol/L versus 0.356±0.138 μmol/L in the female kidney (not significant). The Vmax in the male kidney was 22.4±1.10 pmol 2MeOE·min⁻¹·mL⁻¹ per gram versus 28.5±2.49 pmol 2MeOE·min⁻¹·mL⁻¹ per gram in the female kidney (small but significant difference). In the male kidney, the
V_{\text{max}}/K_m was 56.2±4.30 pmol 2MeOE·min^{-1}·mL^{-1}·μmol/L^{-1} per gram versus 112±32.3 pmol 2MeOE·min^{-1}·mL^{-1}·μmol/L^{-1} per gram in the female kidney (not significant).

The mesenteric vascular bed had little ability to methylate 2OHE (Figure 1). At 0.1 μmol/L 2OHE, the amount of 2MeOE produced was only 0.104±0.009 and 0.179±0.03 nmol 2MeOE/5 min in the male and female, respectively. In the male mesenteric vascular bed, the K_m was 0.530±0.110 μmol/L versus 0.438±0.167 μmol/L in the female mesenteric vascular bed (not significant). The V_{\text{max}} in the male mesentery was 1.19±0.19 pmol 2MeOE·min^{-1}·mL^{-1} per gram versus 0.726±0.168 pmol 2MeOE·min^{-1}·mL^{-1} per gram in the female mesentery (P<0.05 vs male and female hearts and kidneys). The V_{\text{max}}/K_m in the male mesentery was 2.46±0.320 pmol 2MeOE·min^{-1}·mL^{-1}·μmol/L^{-1} per gram versus 2.07±0.483 pmol 2MeOE·min^{-1}·mL^{-1}·μmol/L^{-1} per gram in the female (P<0.05 vs male and female hearts and kidneys).

When expressed as conversion per total organ, the kidney had the greatest capacity to methylate 2OHE, with a V_{\text{max}} of 41.0±2.70 and 36.4±7.27 pmol 2MeOE·min^{-1}·mL^{-1} in the male and female, respectively, followed by the heart, which had a V_{\text{max}} of 25.2±2.60 and 24.3±1.51 pmol 2MeOE·min^{-1}·mL^{-1} in the male and female, respectively. The male and female mesenteries had a V_{\text{max}} of 3.99±0.60 and 2.40±0.558 pmol 2MeOE·min^{-1}·mL^{-1}.

Disregarding urinary excretion of 2MeOE and combining both males and females, the efficiency of 2OHE methylation was as high as 41% in the coronary circulation and 38% in the kidney, with the lower concentration of 2OHE used (0.1 μmol/L). At higher concentrations of 2OHE, the efficiency of conversion was either the same in the heart and the kidney or slightly higher in the kidney (Table). The percentage conversion of 2OHE to 2MeOE decreased with increasing concentrations of 2OHE. For example, in the heart at concentrations of 0.3, 1, and 3 μmol/L 2OHE, the percentage conversion was 28.8±2.79, 10.9±0.919, and 3.74±0.198, respectively, and in the kidney at 0.3, 1, and 3 μmol/L 2OHE, the percentage conversion was 28.9±2.16, 13.2±1.16, and 5.79±0.445, respectively. In the mesentery the percentage conversion was very low compared with the percentage conversion in the coronary circulation (heart) and kidney, and even at 0.1 μmol/L of 2OHE, the percentage conversion was only 5.17±0.610, about 7 times less than in the kidney and 8 times less than the heart. At 0.3, 1, and 3 μmol/L, the percentage conversion in the mesentery was 2.83±0.315, 1.30±0.132, and 0.642±0.079, respectively.

Our previous in vitro experiments demonstrate that 2OHE methylation is COMT-dependent. We therefore examined whether in the male kidney 2OHE is mainly methylated via a COMT-dependent pathway. Methylation of 2OHE was concentration-dependent for 0.1 to 10 μmol/L 2OHE. At these concentrations, methylation was blocked by quercetin (10 μmol/L), a competitive inhibitor of COMT (Figure 3). Quercetin blocked the methylation of 2OHE by 51.8±7.50%, 86.3±2.60%, 88.9±1.00%, 87.2±1.50%, and 84.8±1.30% for the 0.1, 0.3, 1, and 10 μmol/L concentrations of 2OHE, respectively (P<0.05).

Catecholamines are endogenous substrates of COMT and could potentially inhibit the metabolism of 2OHE in the kidney. We therefore examined in the male and female kidney whether exogenous catecholamines block the 2OHE methylation pathway in the kidney. Indeed, in the male kidney, norepinephrine at concentrations of 10, 30, and 100 μmol/L inhibited methylation of 0.3 μmol/L 2OHE by 40.9±2.40%, 47.8±4.40%, and 57.5±1.80%, respectively.

**Efficiency of Conversion of 2OHE to 2MeOE in the Combined Male and Female Perfused Kidney**

<table>
<thead>
<tr>
<th>Concentration of 2OHE Infused</th>
<th>Heart</th>
<th>Kidney</th>
<th>Mesentery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 μmol/L</td>
<td>40.6±2.90†</td>
<td>38.5±3.91†</td>
<td>5.17±0.610</td>
</tr>
<tr>
<td>0.3 μmol/L</td>
<td>28.8±2.79†</td>
<td>28.9±2.16†</td>
<td>2.83±0.315</td>
</tr>
<tr>
<td>1 μmol/L</td>
<td>10.9±0.919†</td>
<td>13.2±1.16†</td>
<td>1.30±0.132</td>
</tr>
<tr>
<td>3 μmol/L</td>
<td>3.74±0.198†</td>
<td>5.79±0.445†</td>
<td>0.642±0.079</td>
</tr>
</tbody>
</table>

*The efficiency of conversion of 2OHE to 2MeOE is expressed as a percentage of infused substrate in the combined male and female perfused kidney and heart, and in the mesentery at 0.1–3 μmol/L 2OHE. Data are mean±SEM (n=10).*

**Figure 2.** Comparison of the apparent K_m, V_{\text{max}}, and V_{\text{max}}/K_m ratio values for the metabolism of 2OHE in the 3 perfused organs in male and female rats. Values represent mean±SEM (male n=6, female n=5). *P<0.05 vs heart; #P<0.05 vs mesentery.

**Figure 3.** Concentration-dependent metabolism of 2OHE (0.1 to 10 μmol/L) and inhibition by quercetin (10 μmol/L) in the perfused male kidney. After equilibration, rat kidneys were perfused with Tyrode’s solution containing 0.1, 0.3, 1, 3, and 10 μmol/L 2OHE with or without 10 μmol/L quercetin. For each concentration, the kidney was perfused for 10 minutes for equilibration before collecting perfusate for another 10 minutes. Values represent mean±SEM (n=6). *P<0.05 vs quercetin.
Inhibition of 2OHE (0.1 μmol/L) methylation in the perfused male kidney by electrical stimulation of renal artery nerve at 12 Hz for 8 minutes (n=6). Values represent mean±SEM. *P<0.05 vs stimulated. The kidney was perfused with Tyrode’s solution containing 0.3 μmol/L 2OHE and 0.57 mmol/L ascorbic acid, with or without 10 μmol/L norepinephrine or epinephrine, and the kidney was perfused for another 20 minutes, again collecting the last 10 minutes of perfusate. The same procedure was repeated for the 30 and 100 μmol/L concentrations of EPI or NE. Female kidneys were similarly perfused, but with 0.05 μmol/L 2OHE and 0.5 μmol/L EPI. Values represent mean±SEM (for n=5 to 6 observations). *P<0.05 vs treated.

(P<0.05). Epinephrine at the same concentrations had effects similar to norepinephrine (Figure 4A). At 10, 30, and 100 μmol/L epinephrine, methylation of 2OHE was inhibited by 52.4±5.03%, 53.9±8.00%, and 66.6±5.05%, respectively (P<0.05). In the female kidney (Figure 4B), a concentration of epinephrine of 0.5 μmol/L inhibited methylation of 0.05 μmol/L 2OHE by 23.7±3.98% (P<0.05).

To examine the physiologically relevant effect of catecholamines as inhibitors of the 2OHE methylation pathway, endogenous norepinephrine was released by electrical stimulation of the renal artery in the perfused male kidney. Continuous stimulation of the nerves in the renal artery at 12 Hz inhibited methylation of 0.1 μmol/L 2OHE by an average of 16.6±1.80% over the 8-minute period of stimulation (Figure 5). The inhibition was persistent for at least 8 minutes. In one experiment the inhibition was as high as 40% during the first 2 minutes of nerve stimulation.

Discussion
Cardiovascular and renal diseases are mediated in part by inappropriate cell proliferation caused by growth stimuli such as mechanical injury, oxidative stress, or pro-proliferative biomolecules. Consequently, appropriate concentrations of endogenous antimitogenic molecules to prevent cell proliferation are essential to attenuate the development and progression of cardiovascular and renal diseases.

2MeOE is a potent endogenous antimitogenic molecule produced via methylation of 2OHE, thus rendering this pathway an important growth regulatory mechanism. In this regard, previous findings in our laboratory indicate that glomerular mesangial, vascular smooth muscle, and endothelial cells (coronary and aortic) are capable of methylating 2OHE.8,15 Moreover, our data indicate that this pathway inhibits cell proliferation and collagen synthesis and is blocked by classical COMT inhibitors and catecholamines.6,7

In the present study, we examined the 2OHE methylation pathway in the intact kidney, heart (coronary circulation), and mesentery. Our results suggest that this pathway is a robust and efficient process in the heart and kidney. Further, our results indicate that there are no differences between male and female with respect to the efficiency of the 2OHE methylation pathway in the heart and kidney. In contrast to the heart and kidney, the mesenteric vascular bed has little capacity to convert 2OHE to 2MeOE.

At the lowest and more physiologically relevant 2OHE concentration used (0.1 μmol/L), the percentage conversion of 2OHE to 2MeOE was highest in the heart and kidney (41% in heart vs 38% in kidney vs 5% in the mesentery). The higher efficiency of conversion in the heart and the kidney compared with the mesentery is predictable given the lower Km in the heart and kidney and the higher Vmax/Km ratio value of the heart and kidney compared with the mesentery. Expressed per whole organ, the kidney maintains higher capacity to metabolize 2OHE, as indicated by the higher Vmax. The results of the present study confirm our previous findings in coronary and aortic smooth muscle cells and endothelial cells in culture. In this regard, COMT in coronary cells has a lower Km for 2OHE and a higher Vmax/Km than aortic cells, and coronary cells are thus more efficient in metabolizing 2OHE.8

The 2OHE methylation pathway in the kidney is blocked by quercetin (a known inhibitor of COMT) by nearly 90%, indicating a COMT-dependent methylation of 2OHE. The catecholamines, norepinephrine and epinephrine, also inhibit methylation of 2OHE in the kidney, with the 2 catecholamines showing about the same order of potency as in cultured cells.7 Stimulation of periarterial nerves with the consequent release of endogenous norepinephrine also causes a marked inhibition of 2OHE methylation. This is of notable physiological significance because we show not only that exogenous catecholamines can inhibit 2OHE methylation, but also that local release of norepinephrine in the neuroeffector junction can inhibit 2OHE methylation.
In the present study, we employed a monoamine oxidase inhibitor (pargyline) and a norepinephrine re-uptake inhibitor (desipramine) to enhance diffusion of endogenous norepinephrine through the kidney. In this regard, detection of inhibition of 2OHE methylation by periarterial nerve stimulation in the absence of these inhibitors would have been possible only with very low concentrations of 2OHE because the interaction between 2OHE and norepinephrine at COMT is competitive. Because of the sensitivity limitations of our high-performance liquid chromatography method, lower concentrations of 2OHE could not have been used. Importantly, the re-uptake inhibitor desipramine is an α1-adrenoceptor antagonist. Consequently, on renal artery stimulation and release of norepinephrine, there were no changes in perfusion pressure or renal vascular resistance. Therefore, blockade of the 2OHE methylation pathway by sympathetic nerve stimulation in the kidney was not secondary to changes in renal hemodynamics but most likely was mediated by competition between 2OHE and endogenous norepinephrine for COMT. The fact that endogenous norepinephrine can inhibit 2OHE methylation, together with the fact that increased catecholamines are related to renal diseases,16–18 provides evidence that one possible mechanism by which catecholamines accelerate renal disease is by inhibiting methylation of 2OHE, thus abrogating the antiproliferative effect of 2MeOE.

Our findings that methylation of 2OHE is inhibited by catecholamines may be of pathophysiologically relevance. Evidence suggests that catecholamines contribute to the process of glomerulosclerosis16–18 and vaso-occlusive disorders.11,19–21 In a model of chronic renal failure induced by renal ablation, renal afferent denervation by dorsal rhizotomy retarded the progression of glomerulosclerosis/proliferation.17 Furthermore, in rats with reduced renal mass, administration of moxonidine at doses that do not cause hypotension but inhibit sympathetic nerve traffic reduced glomerulosclerosis.18 The sympathetic nervous system is activated in patients with the nephrotic syndrome (normal creatinine clearance) compared with normal individuals. These patients not only have higher plasma norepinephrine but also have increased renal excretion of norepinephrine.16

Premenopausal women have lower incidence of both renal and cardiovascular diseases.22–24 This suggests that the presence of an active 2OHE methylation pathway in the kidney and heart in premenopausal women may be responsible for protection against renal and vascular damage. Further, women under chronic stress, which results in increased catecholamines, may not be protected by 17β-estradiol because the interaction between 2OHE and norepinephrine at COMT is competitive. Because of the sensitivity limitations of our high-performance liquid chromatography method, lower concentrations of 2OHE could not have been used. Importantly, the re-uptake inhibitor desipramine is an α1-adrenoceptor antagonist. Consequently, on renal artery stimulation and release of norepinephrine, there were no changes in perfusion pressure or renal vascular resistance. Therefore, blockade of the 2OHE methylation pathway by sympathetic nerve stimulation in the kidney was not secondary to changes in renal hemodynamics but most likely was mediated by competition between 2OHE and endogenous norepinephrine for COMT. The fact that endogenous norepinephrine can inhibit 2OHE methylation, together with the fact that increased catecholamines are related to renal diseases,16–18 provides evidence that one possible mechanism by which catecholamines accelerate renal disease is by inhibiting methylation of 2OHE, thus abrogating the antiproliferative effect of 2MeOE.

The mesentery is not as frequently affected by severe vaso-occlusive disorders as is the heart and kidney, which may explain why high levels of COMT activity in the mesentery are not necessary. The heart and kidney have higher capacity to metabolize 2OHE, and this could be a potential mechanism for estradiol-induced cardiovascular and renoprotection during the reproductive age in women. The low Km in the heart assures that even low concentrations of 2OHE will be metabolized and confer protection. This may further explain the low rates of coronary heart disease in women during the reproductive years.

Our findings that local release of catecholamines in the kidney inhibit 2OHE methylation may be of broader pathophysiological relevance. In this regard, our results imply that activation of the sympathetic nerves in other innervated vascular beds could also inhibit 2OHE metabolism. Because the 2OHE methylation pathway is an active antimitogenic, antifibrotic pathway,6 our results suggest that the initiation/progression of vaso-occlusive disorders in other vascular beds may, in part, be mediated through decreased methylation of 2OHE, and hence, reduced protection from cell proliferation. In addition, in this study the inhibition was the result of norepinephrine diffusing to the whole kidney, as a result of the use of monoamine oxidase (MAO) and re-uptake inhibitors. This implies that the high levels of norepinephrine normally achieved in neuroeffector junctions would effectively inhibit 2OHE methylation in the junction.

The high methylation of 2OHE in the heart may ensure that not only coronary arteries are protected but also cardiac tissue. The high amounts of 2MeOE produced in the coronary
Our results indicate that increased catecholamines in these patients may further worsen heart failure by abrogating the anti-angiogenic and anti-fibrotic effects of 2OH-E by preventing its metabolism.

In summary, we provide evidence that the 2OH-E methylation pathway is present in the kidney, heart, and mesentery. This pathway is efficient in the heart and the kidney, but inefficient in the mesentery. Furthermore, we provide evidence that exogenous and endogenous catecholamines inhibit methylation of 2OH-E in the kidney. Given the adverse effects of catecholamines in the cardiovascular and renal systems, our results imply that inhibition of this pathway by catecholamines may contribute to the progression of cardiorenal diseases.

Perspectives
Our results suggest that the conversion of 17β-estradiol to 2OH-E and then to 2MeOE may be an important determinant of the cardiorenal protective effects of circulating 17β-estradiol and that individual differences in the local formation of 2MeOE could influence a woman’s risk of renal and cardiovascular disease. Thus, genetic, acquired, or tissue-specific differences in COMT activity may determine the benefits a woman receives from either endogenous 17β-estradiol in the premenopausal state or exogenous 17β-estradiol from replacement therapy in the postmenopausal state. The fact that local release of catecholamines inhibits the conversion of 2OH-E to 2MeOE by competing for COMT suggests that pathological increases in catecholamine release may also influence an individual woman’s risk of renal and cardiovascular disease. Specifically, chronic stress or other disease states that elevate catecholamines may limit methylation of 2OH-E, and this may worsen the progression of renal and cardiovascular proliferative diseases. Future studies should examine the relationship between catecholamine levels and the production rate of 2MeOE in women.

References