Vascular responses in vivo to 8-epi PGF$_{2\alpha}$ in normal and hypercholesterolemic pigs

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Krier, James D., Martin Rodriguez-Porcel, Patricia J. M. Best, J. Carlos Romero, Amir Lerman, and Lilach O. Lerman. Vascular responses in vivo to 8-epi PGF$_{2\alpha}$ in normal and hypercholesterolemic pigs. Am J Physiol Regulatory Integrative Comp Physiol 283: R303–R308, 2002. First published May 6, 2002; 10.1152/ajpregu.00602.2001.—Hypercholesterolemia (HC) is characterized by increased circulating 8-epi-prostaglandin-F$_{2\alpha}$ (isoprostane), a vasoconstrictor, marker, and mediator of increased oxidative stress, whose vascular effects might be augmented in HC. Anesthetized pigs were studied in vivo with electron beam computed tomography after a 12-wk normal (n = 8) or HC (n = 8) diet. Mean arterial pressure (MAP), single-kidney perfusion, and glomerular filtration rate (GFR) were quantified before and during unilateral intrarenal infusions of U46619 (10 ng·kg$^{-1}$·min$^{-1}$) or isoprostane (1 µg·kg$^{-1}$·min$^{-1}$). Basal renal perfusion and function were similar, and isoprostane infusion elevated its systemic levels similarly in normal and HC (333 ± 89 vs. 366 ± 48 pg/ml, respectively, P < 0.01 vs. baseline). Both drugs markedly and comparably decreased cortical perfusion and GFR in both groups, whereas medul- lary perfusion decreased significantly only in HC. Moreover, MAP increased significantly only in HC (+9 ± 3 vs. +11 ± 3 mmHg, respectively, P = 0.05). Hence, in HC, renal functional responses to high-dose isoprostane are largely similar to normal, but the systemic circulation exhibits augmented sensitivity to pathophysiological levels of isoprostane and U46619, which may potentially play a role in development of hypertension and vascular injury associated with increased oxidative stress.

Hypercholesterolemia; glomerular filtration rate

Hypercholesterolemia (HC) is a common cardiovascular risk factor that impairs vascular function before development of overt atherosclerosis. One of the mechanisms by which HC may induce functional and structural alterations is instigation of reactive oxygen species formation, or increased oxidative stress, in association with lipid peroxidation (26). A recently discovered series of prostaglandin (PG) F$_{2\alpha}$-like compounds, 8-epi PGF$_{2\alpha}$ (isoprostane), are produced in vivo by nonenzymatic free radical catalyzed peroxidation of arachidonic acid (26), as may occur during oxidation of low-density lipoprotein (LDL). Plasma levels of isoprostane are elevated in HC humans (6, 29) and pigs (3, 33, 42) and represent novel markers of endogenous lipid peroxidation and oxidant status in vivo (30). Moreover, isoprostane can exert potent biological activity such as vasoconstriction (18), and it has been proposed to mediate oxidant injury (30) and contribute to the vascular pathobiology associated with atherosclerosis (24).

The kidney is susceptible to abnormal lipid metabolism, which may modify and accelerate glomerular and vascular damage. We previously showed that swine diet-induced HC was associated with impaired functional responses to challenge of the renal vasculature in vitro (36, 37) and renal perfusion in vivo (8, 32). Imbalance between vasodilators and vasoconstrictors, increased oxidative stress (34), or enhanced response to vasoconstrictors like isoprostane (8) may contribute to functional and eventually structural vascular and renal injury in HC. However, it is yet unknown whether the HC kidney exhibits abnormal responses to isoprostane.

Electron beam computed tomography (EBCT) is an ultrafast scanner that allows reliable, noninvasive quantifications of single-kidney regional perfusion and glomerular filtration rate (GFR) (17). This technique thus allows a unique opportunity to study the direct effect of isoprostane on the in vivo intact pig kidneys. Therefore, the present study was designed to examine whether in HC pigs intrarenal perfusion and function show differential responses to isoprostane compared with normal, and furthermore, whether such responses were selective to isoprostane or shared by a thromboxane (Tx) receptor agonist.

METHODS

This study was performed according to Institutional Animal Care and Use guidelines. Domestic female pigs (55–65 kg) were studied with EBCT after 12 wk of either a normal (n = 8) or HC diet (n = 8) consisting of 2% cholesterol (Harlan Teklad, Madison, WI) (8). EBCT studies. On the day of the EBCT study, each animal was anesthetized with 0.5 g of intramuscular ketamine and...
xylazine, intubated, and mechanically ventilated with room air. Anesthesia was maintained with a mixture of ketamine (0.2 mg·kg⁻¹·min⁻¹) and xylazine (0.03 mg·kg⁻¹·min⁻¹) in normal saline, and it was administered via an ear vein cannula at a rate of 0.05 ml·kg⁻¹·min⁻¹. Under sterile conditions and fluoroscopic guidance, an 8F arterial guide was inserted in the left carotid artery and advanced to the abdominal aorta; a pigtail catheter was advanced within the guide and positioned in the midsection of the left renal artery. The arterial guide was maintained at a level above the scanning plane and served for monitoring mean arterial pressure (MAP) throughout the experiment. A pigtail catheter was advanced through a jugular vascular sheath and positioned in the superior vena cava or right atrium for subsequent contrast media injections, and another suprapubic catheter was placed in the urinary bladder for urine collection. Saline infusion (3–4 ml/min) was initiated into a side arm of the venous vascular sheath, and electrocardiogram leads served for monitoring heart rate.

After catheter placement, each animal was positioned in the EBCT workstation, transferred, and displayed on a Sun workstation. The densities of the aorta, cortex, medulla, and papilla were sampled after manually tracing these regions of interest. Time-density curves were generated for each region and fitted with extended gamma-variate curve fit, as previously described (8, 17, 32). After completion of all studies, the pigs were euthanized with a lethal infusion of Sleepaway (Fort Dodge Laboratories, Fort Dodge, IA).

EBCT data analysis. All images were reconstructed on the EBCT workstation, transferred, and displayed on a Sun workstation. The densities of the aorta, cortex, medulla, and papilla were sampled after manually tracing these regions of interest. Time-density curves were generated for each region and fitted with extended gamma-variate curve fit, as previously described (17). Renal regional perfusion (ml/min per cm³ tissue) was then calculated as: 60 × vascular blood volume/mean transit time (17, 32). Normalized single-kidney GFR (ml/min per cm³ tissue) was calculated as: 60 × kidney volume × slope of the accumulation of contrast in the proximal tubule × mean transit time/area under the aortic input curve (17, 32).

Statistical analysis. Results are means ± SE. Comparisons between experimental periods were performed by paired Student’s t-test, and between groups using unpaired t-test, with the Bonferroni correction for multiple comparisons. Statistical significance was determined at P ≤ 0.05.

RESULTS

Systemic parameters. Total cholesterol levels were significantly higher in HC compared with normal pigs (395 ± 60 vs. 67 ± 7 mg/dl, P < 0.001), as were LDL levels (P < 0.001). Plasma TBARS were significantly higher in HC compared with normal (3.7 ± 0.1 vs. 3.2 ± 0.2 nmol/ml, P < 0.05), and total plasma isoprostane tended to be elevated as well (123 ± 13 vs. 98 ± 13 pg/ml, P = 0.09). Basal MAP was significantly lower in HC pigs (Table 1), whereas heart rate was similar. Plasma creatinine levels were significantly higher in HC compared with normal (1.9 ± 0.1 vs. 1.6 ± 0.1 mg/dl, P < 0.05), whereas PRA was similar in both groups (P = 0.2; Table 1).

Infusion of isoprostane elevated systemic total plasma isoprostane to similar levels (P = 0.4) in the normal and HC groups (333 ± 89 vs. 366 ± 48 pg/ml, respectively, P < 0.01 compared with baseline). During infusion of both U46619 and isoprostane, MAP increased significantly only in HC pigs (+11 ± 3 and +9 ± 3 mmHg, respectively, P = 0.013 and P = 0.029 compared with baseline). The magnitude of this increase was significantly greater than that observed in normal pigs (P = 0.05 and P = 0.02 vs. normal) whose MAP remained unaltered (P = 0.4 for both; Table 1 and Fig. 1). The increased MAP in HC pigs was associated with a significant decrease in heart rate (P = 0.003 and P = 0.007, respectively; Table 1), which remained unaltered in normal pigs (P = 0.2 and P = 0.4, respectively). Urinary flow rate was similar between the groups at baseline and slightly increased in HC pigs during isoprostane infusion (Table 1). Creatinine excretion was higher in HC pigs at baseline, but it decreased significantly in this group in response to both...
Table 1. Systemic characteristics of normal and hypercholesterolemic pigs under resting conditions and during randomized intrarenal infusions of the thromboxane receptor agonist U46619 (10 ng·kg⁻¹·min⁻¹) or isoprostane (1 μg·kg⁻¹·min⁻¹)

<table>
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<tr>
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<th>Normal</th>
<th>Hypercholesterolemia</th>
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<tbody>
<tr>
<td><strong>Mean arterial pressure, mmHg</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>114.3 ± 5.8</td>
<td>97.8 ± 3.7†</td>
</tr>
<tr>
<td>U46619</td>
<td>114.9 ± 4.7</td>
<td>108.6 ± 5.0*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>115.5 ± 3.7</td>
<td>106.9 ± 5.1*</td>
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<tr>
<td><strong>Heart rate, beats/min</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>85.1 ± 4.9</td>
<td>82.8 ± 4.0</td>
</tr>
<tr>
<td>U46619</td>
<td>83.2 ± 4.9</td>
<td>73.0 ± 4.3*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>86.1 ± 5.0</td>
<td>69.9 ± 4.0*†</td>
</tr>
<tr>
<td><strong>Plasma renin activity, ng·ml⁻¹·h⁻¹</strong></td>
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<tr>
<td>Baseline</td>
<td>0.4 ± 0.2</td>
<td>0.9 ± 0.4</td>
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<tr>
<td>U46619</td>
<td>0.4 ± 0.1</td>
<td>0.5 ± 0.3*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.3</td>
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<tr>
<td><strong>Urine flow rate, ml/min</strong></td>
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<tr>
<td>Baseline</td>
<td>4.81 ± 1.33</td>
<td>3.31 ± 0.85</td>
</tr>
<tr>
<td>U46619</td>
<td>4.26 ± 1.31</td>
<td>3.81 ± 1.01</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>4.27 ± 2.35</td>
<td>3.76 ± 0.82*</td>
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<tr>
<td><strong>Creatinine excretion, mg/min</strong></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>1.14 ± 0.21</td>
<td>1.81 ± 0.26†</td>
</tr>
<tr>
<td>U46619</td>
<td>1.70 ± 0.81</td>
<td>1.24 ± 0.18*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>1.61 ± 0.85</td>
<td>1.04 ± 0.14*</td>
</tr>
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Values are means ± SE. *P < 0.05 vs. baseline; †P < 0.05 vs. normal.

Table 2. Bilateral single-kidney hemodynamics and function in normal and hypercholesterolemic pigs under basal conditions and during unilateral intrarenal infusions of the thromboxane receptor agonist U46619 (10 ng·kg⁻¹·min⁻¹) or isoprostane (1 μg·kg⁻¹·min⁻¹)

<table>
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<tr>
<th></th>
<th>Normal</th>
<th>Hypercholesterolemia</th>
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<tbody>
<tr>
<td><strong>Cortical perfusion, ml·min⁻¹·ml tissue⁻¹</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.07 ± 0.35</td>
<td>6.33 ± 0.57</td>
</tr>
<tr>
<td>U46619</td>
<td>1.57 ± 0.79*</td>
<td>1.34 ± 0.41*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>3.95 ± 0.82*</td>
<td>2.95 ± 0.73*</td>
</tr>
<tr>
<td><strong>Medullary perfusion, ml·min⁻¹·ml tissue⁻¹</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.31 ± 1.10</td>
<td>6.26 ± 0.71</td>
</tr>
<tr>
<td>U46619</td>
<td>2.98 ± 1.44*</td>
<td>1.86 ± 0.64*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>3.67 ± 1.34</td>
<td>3.24 ± 0.78*</td>
</tr>
<tr>
<td><strong>Papillary perfusion, ml·min⁻¹·ml tissue⁻¹</strong></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>6.87 ± 0.81</td>
<td>5.93 ± 1.20</td>
</tr>
<tr>
<td>U46619</td>
<td>3.85 ± 0.92*</td>
<td>2.74 ± 0.71*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>4.77 ± 1.14</td>
<td>5.19 ± 0.99</td>
</tr>
<tr>
<td><strong>Glomerular filtration rate, ml·min⁻¹·ml cortical tissue⁻¹</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.55 ± 0.05</td>
<td>0.68 ± 0.08</td>
</tr>
<tr>
<td>U46619</td>
<td>0.16 ± 0.04*</td>
<td>0.17 ± 0.05*</td>
</tr>
<tr>
<td>Isoprostane</td>
<td>0.35 ± 0.09*</td>
<td>0.35 ± 0.07*</td>
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</table>

Values are means ± SE. *P < 0.05 vs. baseline.

Table 1. Systemic characteristics of normal and hypercholesterolemic pigs under resting conditions and during randomized intrarenal infusions of the thromboxane receptor agonist U46619 (10 ng·kg⁻¹·min⁻¹) or isoprostane (1 μg·kg⁻¹·min⁻¹)

Drugs (Table 1). PRA did not increase during either infusion.

Renal hemodynamics and function. Basal single-kidney perfusion and GFR were similar in normal and HC pigs (Table 2). During intrarenal infusion of either U46619 or isoprostane, the significant decreases in GFR of the infused kidneys were comparable in normal

\((-68 \pm 9 \text{ and } -35 \pm 14\% \text{, respectively})\) and HC pigs \((-72 \pm 8 \text{ and } -49 \pm 7\%, \text{ respectively})\). Likewise, U46619 and isoprostane induced similar reductions in regional renal perfusion in both groups. In response to U46619 and isoprostane, cortical perfusion decreased in both normal (by \(-73 \pm 11 \text{ and } -36 \pm 13\%, \text{ respectively})\) and HC (by \(-77 \pm 7 \text{ and } -55 \pm 9\%, \text{ respectively})\); Table 2) pigs. U46619 induced significant reductions in medullary perfusion in both normal and HC \((-55 \pm 17 \text{ and } -67 \pm 12\%, \text{ respectively})\), but a decrease in medullary perfusion in response to isoprostane observed in HC \((-47 \pm 11\%, \text{ P} = 0.004)\) has not reached statistical significance in normal pigs \((-31 \pm 17\%, \text{ P} = 0.07; \text{ Table 2})\). Papillary perfusion decreased significantly in response to U46619 in normal and HC pigs (-44 ± 11 and -54 ± 23%, respectively), whereas isoprostane did not significantly reduce papillary perfusion in either normal or HC pigs (-27 ± 17 and -12 ± 12%, respectively; Table 2).

**DISCUSSION**

This study demonstrates that intrarenal infusion of high-dose isoprostane decreases cortical perfusion and GFR similarly in normal and HC pigs but may induce a greater decline in medullary perfusion in HC. In addition, a greater increase in blood pressure in HC in response to isoprostane may imply increased propensity for systemic vasoconstriction and augmented sensitivity to pathophysiological levels of isoprostane. Similarly, augmented sensitivity was observed in response to the Tx receptor agonist U46619, suggesting...
that these abnormalities were not selective to isoprostane. These effects may potentially play a role in development of hypertension and in vascular injury associated with HC and increased lipid peroxidation.

HC is characterized by attenuated vasodilatory responses and augmented propensity for vasoconstriction (11, 13), as well as by an increase in circulating levels of isoprostane (3, 33, 42), a vasoconstrictor and marker of increased oxidative stress in vivo. In the current study, isoprostane levels in HC pigs tended to increase, and the levels of TBARS, additional markers of increased oxidative stress, were significantly elevated. In addition, in our HC model, systemic LDL oxidizability is markedly increased and systemic endogenous antioxidant defenses markedly decreased (32, 33, 37), indicating increased oxidative stress. We previously showed in the pig model that HC was also associated with an enhanced coronary vasoconstriction response to isoprostane in vitro (43). However, the effect of isoprostane on the systemic circulation in HC in vivo has not been demonstrated. In the renal circulation, HC also induces abnormal vascular responses to challenge, both in vivo (8, 32) and in vitro (36), likely related to increased oxidative stress and lipid peroxidation (32, 37). However, renal responsiveness to isoprostane in HC, or its potential involvement in renal functional abnormalities, has not been evaluated.

The potent vasoconstrictor effect of isoprostane is mediated via a dose-dependent and reversible (39) interaction with vascular Tx/endoperoxide receptor. However, the subsequent downstream signaling mechanisms triggered by isoprostane are largely different from those activated by U46619 (19, 20) and may mediate their specific proatherogenic effects (9, 20). Distinct isoprostane receptor sites on vascular smooth muscle cells may also account for their marked potency (10). Furthermore, unlike primary PGs, which are rapidly metabolized to inactive products, isoprostane circulates in plasma (28) and may hence induce or amplify concurrent pathological processes. Therefore, in HC and atherosclerosis, isoprostane might conceivably have selective and distinct effects and participate in disease progression.

Our study underscores the striking sensitivity of the intact kidney to the direct effects of vasoconstrictor PG (41). Intrarenal infusion of isoprostane or U46619 in both normal and HC pigs induced marked cortical vasoconstriction and decrease in GFR, comparable to the decrease in GFR and renal blood flow previously observed in normal animals in response to similar doses of isoprostane (26) or U46619 (5). Interestingly, most of the functional renal responses to both U46619 and isoprostane were similar in normal and HC pigs. The exception was medullary perfusion that decreased slightly more in HC, possibly reflecting vulnerability of the medullary circulatory to injury involving increased oxidative stress. Indeed, to demonstrate their vasoconstrictor effect on the kidney, the conventional dose of isoprostane infused in the current as well as in previous studies (26, 38) was higher than the basal circulating level that we observed. However, its systemic (31) and intrarenal production is markedly elevated under inflammatory (16) and oxidative stress (23) conditions and may approach the infused concentration. Furthermore, the marked vasoconstriction induced by intrarenal infusion might have conceivably masked subtle differential sensitivity to lower circulating levels of the drugs.

This postulation may be supported by the systemic effects of U46619 and isoprostane observed in HC, implying augmented vascular sensitivity to the drugs. In both groups, intrarenal systemic spillover during isoprostane infusion likely increased their circulating levels similarly, but an increase in MAP and decrease in heart rate were observed in HC alone. Speculatively, the increase in MAP in HC might have led to the small increase in urinary flow rate, whereas an overall decrease in creatinine excretion rate might have resulted from a concurrent decrease in GFR of the contralateral kidney exposed to pathophysiologic circulating levels of the drugs. The reason for the slightly higher basal creatinine excretion rate observed in HC pigs is unclear.

Increased sensitivity to the pressor effects of U46619 has been previously observed in physiological conditions like salt loading and may result from increased abundance and activation of the renal TXA2/PGH2 receptor (40). In HC, enhanced sensitivity to vasoconstrictor PG may be related to endothelial injury, increased production of TXA2 (1), or interaction with coexisting vasoconstrictors (21). The unchanged PRA during infusions (in fact, slight decrease in HC during infusion of U46619) argues against significant involvement of the systemic renin-angiotensin system. On the other hand, decreased bioavailability of nitric oxide and increased production of superoxide, two conditions that characterize HC, enhance activation of the TXA2 receptor and vasoconstriction responses to U46619 in isolated renal afferent arterioles (35).

Notably, despite the potential vasoconstrictor impact of isoprostane and its increased circulating levels in HC, basal MAP in this group was lower than normal (1). HC pigs exhibit enhanced propensity for diuresis and natriuresis in response to challenge (8, 32) and attenuated development of renovascular hypertension (32), possibly related to intrarenal proinflammatory changes (8). Nevertheless, the increase in MAP in HC may also reflect augmented vascular sensitivity to additional more subtle effects, such as platelet activation, vascular remodeling, or nephropathy (23). Although basal isoprostane level in HC was lower than the level that induced the increase in MAP during infusion, the augmented vascular sensitivity in HC may facilitate development of hypertension and vascular injury during more prolonged or comorbid conditions associated with increased oxidative stress. Elevated circulating isoprostane levels similar to those observed during isoprostane infusion can be observed in pathophysiological human conditions such as preeclampsia (22), coronary reperfusion (15), cirrhosis (27), smoking (25), and diabetes (7). HC may hypothetically act in concert with coexisting pathophysiological mechanisms and fa-
cilitate disease progression (32), development of hyper-
tension, and clustering of risk factors. Hence, a poten-
tial role for isoprostane as endogenous mediator of 
hypertension and vascular injury under such condi-
tions cannot be ruled out.

In summary, our study demonstrates an increase in 
artrial pressure in HC pigs in response to pathophys-
ilological systemic levels of isoprostan and U46619, 
supporting a potential role for vasoconstrictor PG in 
development of hypertension in disease states associ-
ated with increased oxidative stress and comorbid or 
chronic conditions. The response of the HC kidney to 
high-dose infusion was comparable to normal, al-
though medullary perfusion may show enhanced re-
response to isoprostane. Furthermore, the similar degree 
of vascular response to isoprostane compared with 
U46619 does not rule out activation of additional down-
stream pathogenic mechanisms by isoprostane. These 
effects may potentially play a role in vascular injury 
associated with abnormal lipid metabolism and in-
creased oxidative stress.

The authors are grateful to the staff of the EBCT for the technical 
assistance with performance of the experiments.

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ate of the American Heart Association. This work has been pre-
presented in part at the 16th Annual Scientific Meeting of the American 

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