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

James D. Krier, MS$^1$
Martin Rodriguez-Porcel, MD$^2$
Patricia J.M. Best, MD$^2$
J. Carlos Romero, MD$^3$
Amir Lerman, MD$^2$
Lilach O. Lerman, MD, PhD$^1$

From the Department of Internal Medicine, Divisions of Hypertension$^1$ and Cardiovascular Diseases$^2$, and the Department of Physiology and Biophysics$^3$, Mayo Clinic, Rochester, MN.

Short title: Renal function and 8-epi Prostaglandin F$_{2\alpha}$

Address for correspondence:
Lilach O. Lerman, MD, PhD, Division of Hypertension, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
E-Mail: Lerman.Lilach@Mayo.Edu Phone #: (507) 255-1929 Fax #: (507) 255-1935

Copyright 2002 by the American Physiological Society.
Abstract

Hypercholesterolemia (HC) is characterized by increased circulating 8-epi-Prostaglandin-F$_{2\alpha}$ (Isoprostone), 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-week 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 intra-renal infusions of U46619 (10ng/kg/min) or Isoprostone (1µg/kg/min). Basal renal perfusion and function were similar, and Isoprostone 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, while medullary perfusion decreased significantly only in HC. Moreover, MAP increased significantly only in HC (+9±3 and +11±3mmHg, respectively, p≤0.05). Hence, in HC renal functional responses to high-dose Isoprostone are largely similar to normal, but the systemic circulation exhibits augmented sensitivity to pathophysiological levels of Isoprostone and U46619, which may potentially play a role in development of hypertension and vascular injury associated with increased oxidative-stress.

Key words: hypercholesterolemia, 8-epi Prostaglandin F$_{2\alpha}$, glomerular filtration rate.
**Introduction**

Hypercholesterolemia (HC) is a common cardiovascular risk factor that impairs vascular function prior to 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$_2$-like compounds, 8-epi PGF$_{2\alpha}$ (Isoprostane), are produced *in vivo* by non-enzymatic 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 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 have previously shown 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 ultra-fast scanner, which 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 intra-renal perfusion and function show differential responses to Isoprostane compared to 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 weeks of either a normal (n=8) or HC diet (n=8) consisting of 2% cholesterol (Harlan Teklad, Madison, Wisconsin) (8). EBCT studies On the day of the EBCT study, each animal was anesthetized with 0.5 g of intra-muscular ketamine and xylazine, intubated, and mechanically ventilated with room air. Anesthesia was maintained with a mixture of ketamine (0.2 mg/kg/min) and xylazine (0.03 mg/kg/min) in normal saline, administered via an ear vein cannula at a rate of 0.05 mL/kg/min. Under sterile conditions and fluoroscopic guidance, an 8F arterial guide was inserted in the left carotid artery and advanced to the abdominal aorta; a tracker catheter was advanced within the guide and positioned in the mid-section 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 supra-pubic 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 ECG leads served for monitoring heart rate.

Following catheter placement, each animal was positioned in the EBCT (Imatron C-150, Imatron Inc. South San Francisco, CA) scanning gantry. After a 1-hour recovery period and intra-renal saline infusion (1 mL/min), an EBCT study was performed to determine baseline renal hemodynamics and function in both kidneys, as described below. Two additional and
similar EBCT studies were then performed at 30-minute intervals, each after a 10-minute randomized infusion of either the Tx receptor agonist U46619 (10 ng/kg/min) (5) or Isoprostane (1 µg/kg/min) (26, 38). Intra-renal saline infusion was resumed between studies.

Urine was collected for 5 minutes before each EBCT study for determination of urinary flow rate (using a graduated cylinder) and creatinine (spectrophotometry) excretion. A blood sample was collected from the superior vena cava in the middle of the baseline and Isoprostane infusion collection periods for measurement of Isoprostane. The sample obtained at baseline was also used to measure lipid profile (Roche, Nutley, NJ), thiobarbituric acid reactive substances (TBARS) using the colorimetric method (21), electrolytes (flame photometry), and plasma renin activity (PRA, New England Nuclear, Boston, MA).

PGF$_{2\alpha}$-isoprostanes were measured in blood samples that were collected in EDTA tubes, separated, and the plasma stored at -80°C until the time of assay. The total levels of Isoprostane were measured with an enzyme immunoassay kit (EIA, Cayman) for 8-iso-PGF$_{2\alpha}$ (2), as previously described (12, 21). Briefly, prior to the enzyme immunoassay, an alkaline hydrolysis was utilized, and plasma samples purified by Sep-Pak C-18 columns (Milford, MA). The samples, tracer, and antiserum were added to wells pre-coated with mouse monoclonal antibody, and the plates washed to remove all unbound reagents. Ellman’s Reagent (containing the substrate to acetylcholinesterase) was added to the wells. The intensity of the distinct yellow color produced by this enzymatic reaction was determined using a spectrophotometer at 405 nm. This assay has high accuracy as determined by a standard curve plotted using a 4-parameter fit, with a correlation coefficient of 0.99 (4, 14). Standard solution concentrations (5-500 pg/tube) show 91.2±0.6 to 26.7±0.5 % binding, respectively, with a specificity of 98%. The inter-assay variability, tested by running controls over an 18-month period, is less than 10% (4).

**EBCT scanning sequence** Each EBCT study was performed during respiratory suspension at
end-expiration. Using localization scans two mid-hilar tomographic levels of the left kidney were selected. For the study of renal perfusion and function, the kidney was scanned in the multi-slice flow mode (50 msec/image), resulting in two contiguous 8-mm thick mid-hilar sections. Forty consecutive scans (over 3 minutes) were initiated and performed at variable time intervals four seconds after a central venous bolus injection (0.5 cc/kg over 1 sec) of the non-ionic, low-osmolar contrast medium iopamidol (Iovue® -370, Squibb Diagnostics, Princeton, NJ), as previously described (8, 17, 32). Following completion of all studies the pigs were euthanized with a lethal infusion of Sleepaway® (Fort Dodge Laboratories, Inc, 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 X vascular blood volume/mean transit time (17, 32). Normalized single-kidney GFR (mL/min per cm³ tissue) was calculated as: 60 x kidney volume x slope of the accumulation of contrast in the proximal tubule x mean transit time / area under the aortic input curve (17, 32).

**Statistical Analysis.** Results are mean ± SEM. Comparisons between experimental periods were performed by paired Student 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 to 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 to 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), while heart rate was similar. Plasma creatinine levels were significantly higher in HC compared to normal (1.9±0.1 vs. 1.6±0.1 mg/dl, p<0.05), while PRA was similar in both groups (Table 1, p=0.2).

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 to 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 to 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 (Table 1, Figure 1, p=0.4 for both). The increased MAP in HC pigs was associated with a significant decrease in heart rate (Table 1, p=0.003 and p=0.007, respectively), 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 decreased significantly in this group in response to both 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 intra-renal infusion of either U46619 or Isoprostane, the significant decreases in GFR of the infused kidneys were comparable in normal (-68±9 and –35±14 %, respectively) and HC pigs (-72±8 and -49±7 %, 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±11 and -36±13 %, respectively) and HC (by -77±7 and -55±9 %, respectively, Table 2) pigs. U46619 induced significant reductions in medullary perfusion in both normal and HC (-55±17 and –67±12 %, respectively), but a decrease in medullary perfusion in response to Isoprostane observed in HC (-
47±11 %, p=0.004) has not reached statistical significance in normal pigs (-31±17 %, p=0.07, Table 2). Papillary perfusion decreased significantly in response to U46619 in normal and HC pigs (-44±11 and –54±23 %, respectively), while 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 intra-renal 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 have previously shown in the pig model that HC was also associated with 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 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 pro-atherogenic effects (9, 20). Distinct Isoprostane receptor sites on vascular smooth muscle cells may also account for their marked potency (10). Furthermore, unlike primary prostaglandins, 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). Intra-renal 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 intra-renal production is markedly elevated under inflammatory (16) and oxidative stress (23) conditions, and may approach the infused
concentration. Furthermore, the marked vasoconstriction induced by intra-renal 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 intra-renal systemic spillover during Isoprostane infusion likely increased their circulating levels similarly, but an increase in MAP and decrease in heart rate was observed in HC alone. Speculatively, the increase in MAP in HC might have led to the small increase in urinary flow rate, while an overall decrease in creatinine excretion rate might have resulted from a concurrent decrease in GFR of the contralateral kidney exposed to pathophysiological 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 co-existing 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 intra-renal pro-inflammatory 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 co-morbid 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 co-existing pathophysiological mechanisms and facilitate disease progression (32), development of hypertension, and clustering of risk factors. Hence, a potential role for Isoprostane as endogenous mediator of hypertension and vascular injury under such conditions cannot be ruled out.

In summary, our study demonstrates an increase in arterial pressure in HC pigs in response to pathophysiologic systemic levels of Isoprostane and U46619, supporting a potential role for vasoconstrictor PG in development of hypertension in disease states associated with increased oxidative stress and co-morbid or chronic conditions. The response of the HC kidney to high-dose infusion was comparable to normal, although medullary perfusion may show enhanced response to Isoprostane. Furthermore, the similar degree of vascular response to Isoprostane compared to U46619 does not rule out activation of additional downstream pathogenic mechanisms by Isoprostane. These effects may potentially play a role in vascular injury associated with abnormal lipid metabolism and increased oxidative stress.
Acknowledgements

This study was supported by grant number HL-63282 from the National Institutes of Health, and grant number 99603367 from the Northland Affiliate of the American Heart Association. The authors are grateful to the staff of the EBCT for the technical assistance with performance of experiments. This work has been presented in part at 16th Annual Scientific Meeting of the American Society of Hypertension in May 2001.

Figure Legends

Figure 1. Change in mean arterial pressure (MAP) from baseline during intra-renal infusions of the thromboxane receptor agonist U46619 (black bars) or Isoprostane (gray bars) in normal and hypercholesterolemic pigs. * p<0.05 vs. baseline.
**Table 1.**

Systemic characteristics of normal and hypercholesterolemic pigs under resting conditions and during randomized intra-renal infusions of the thromboxane receptor agonist U46619 (10 ng/kg/min) or Isoprostane (1µg/kg/min).

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Arterial Pressure (mmHg)</strong></td>
<td></td>
<td></td>
</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>
</tr>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td></td>
<td></td>
</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/hr)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.4±0.2</td>
<td>0.9±0.4</td>
</tr>
<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>
</tr>
<tr>
<td><strong>Urine Flow Rate (ml/min)</strong></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td><strong>Creatinine Excretion (mg/min)</strong></td>
<td></td>
<td></td>
</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>
</tbody>
</table>

* p<0.05 vs. baseline; ¥ p<0.05 vs. normal
Table 2. Bilateral single-kidney hemodynamics and function in normal and hypercholesterolemic (HC) pigs under basal conditions and during unilateral intra-renal infusions of the thromboxane receptor agonist U46619 (10 ng/kg/min) or Isoprostone (1µg/kg/min).

<table>
<thead>
<tr>
<th>Infused Kidney</th>
<th>Normal</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical perfusion (ml/min/cc tissue)</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>Isoprostone</td>
<td>3.95±0.82*</td>
<td>2.95±0.73*</td>
</tr>
<tr>
<td><strong>Medullary perfusion (ml/min/cc tissue)</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>Isoprostone</td>
<td>3.67±1.34</td>
<td>3.24±0.78*</td>
</tr>
<tr>
<td><strong>Papillary perfusion (ml/min/cc tissue)</strong></td>
<td></td>
<td></td>
</tr>
<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>Isoprostone</td>
<td>4.77±1.14</td>
<td>5.19±0.99</td>
</tr>
<tr>
<td><strong>Glomerular Filtration Rate (ml/min/cc cortical tissue)</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>Isoprostone</td>
<td>0.35±0.09*</td>
<td>0.35±0.07*</td>
</tr>
</tbody>
</table>

* p<0.05 vs. baseline
Figure 1.
REFERENCES

1. Bank, N., and H. S. Aynedjian. Role of thromboxane in impaired renal vasodilatation

2. Basu, S. Radioimmunoassay of 8-iso-prostaglandin F2alpha: an index for oxidative injury via
free radical catalysed lipid peroxidation. Prostaglandins Leukot Essent Fatty Acids 58: 319-25,
1998.

endothelial function is preserved with chronic endothelin receptor antagonism in experimental

(abstract)

5. Cirino, M., H. Morton, C. MacDonald, J. Hadden, and A. W. Ford-Hutchinson. Thromboxane
A2 and prostaglandin endoperoxide analogue effects on porcine renal blood flow. Am J Physiol

6. Davi, G., P. Alessandrini, A. Mezzetti, G. Minotti, T. Bucciarelli, F. Costantini, F. Cipollone,
G. B. Bon, G. Ciabattoni, and C. Patrono. In vivo formation of 8-Epi-prostaglandin F2 alpha is

Vitacolonna, T. Bucciarelli, F. Costantini, F. Capani, and C. Patrono. In vivo formation of 8-iso-
prostaglandin f2alpha and platelet activation in diabetes mellitus: effects of improved metabolic

8. Feldstein, A., J. D. Krier, M. Hershman Sarafov, A. Lerman, P. J. M. Best, S. H. Wilson, and


isoprostanes during oxidation of human low-density lipoprotein and plasma by peroxynitrite. 


