Lack of microsomal prostaglandin E synthase-1 reduces cardiac function following angiotensin II infusion

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Angiotensin II (ANG II) is a well-known vasoconstrictor and has been implicated in the cardiac remodeling that occurs in diseases such as hypertension. It is also recognized as a stimulator of prostanoid production, with stimulatory effects on phospholipase A₂, COX-2, and mPGES-1. Historically, PGE₂ was thought to counterbalance or buffer the vasoconstrictor effects of ANG II. This study was designed to test the hypothesis that mPGES-1 is the PGE synthase involved in the production of PGE₂ in the mouse heart that contributes to the development of hypertrophy following ANG II infusion. This hypothesis was tested using mPGES-1 knockout (KO) mice subjected to ANG II infusion for 8 wk followed by determination of cardiac function.

MATERIALS AND METHODS

mPGES-1 KO mice. The mPGES-1 KO mice used in this study have a global deletion of mPGES-1. This line of mice (28) have been backcrossed with the C57Bl/6 strain and provided to us by Pfizer.

Experimental protocol. All animal experiments were approved by the Henry Ford Health System Institutional Animal Care and Use Committee in accordance with federal guidelines. Ten- to 12-wk-old mPGES-1 KO mice and C57BL/6 mice were treated with either vehicle or ANG II for a period of 8 wk. Echocardiography was performed on conscious animals before surgery and at 8 wk postinfusion. Blood pressure was monitored on a biweekly basis to ensure that all animals receiving ANG II exhibited the expected increase in systolic blood pressure. At the end of the study, animals were anesthetized with pentobarbital sodium (100 mg/kg ip), and the heart was injected with 15% potassium chloride, leading to its arrest in diastole. The heart was removed and washed in ice-cold PBS, and the atria and right ventricle were dissected. If hearts were used for RNA extraction, they were stored in RNALater at −80°C. For histological analysis, hearts were frozen in OTC media prechilled in isopentane and stored at −80°C. For protein extraction, pieces of heart were snap-frozen in liquid N₂ and stored at −80°C.

Blood pressure measurements. Blood pressure was measured on a biweekly basis using the tail cuff method. Systolic blood pressure was
obtained by the tail cuff method using a MC 4000 blood pressure analysis system for mice (Hatters Instruments, Cary, NC). Briefly, mice were pretrained for at least 1 wk before analysis. They were maintained at 38–39°C and subjected to 10 cycles of blood pressure analysis. At least seven good readings in a cycle of 10 measurements were needed to accept the measurements. In addition, a minimum systolic value of >75 mmHg was set as an exclusion criterion.

**Echocardiography.** Echocardiography was performed on conscious animals before surgery and at 8 wk postinfusion. The cardiac function of all mice was assessed by echocardiography using an Acuson 256 system (Mountain View, CA) with a 15-MHz linear transducer, as reported previously (23). Mice were conscious during the procedure. Diastolic measurements were made at the maximum left ventricle cavity dimension, whereas systolic parameters were measured during maximum anterior motion of the posterior wall. All echocardiography was performed by the same investigator who was blinded to the genotype.

**Infusion of ANG II by osmotic minipump.** ANG II (Bachem, Torrance, CA) was dissolved in 0.01 N acetic acid diluted in physiological saline and given at a dose of 1.4 mg·kg⁻¹·day⁻¹ sc using osmotic minipumps. Control mice received vehicle. Mice at 10–12 wk of age were anesthetized with pentobarbital sodium, and an osmotic minipump was implanted under the skin. At the end of 8 wk, the pump was removed and replaced with a new pump for a further 4 wk.

**Histology.** Mouse hearts were harvested and sectioned transversely into four slices from apex to base (sections A–D). The sections were frozen in isopentane and stored at −70°C for determination of collagen fraction and myocyte cross-sectional area (MCSA). For MCSA, sections of the heart were double-stained with fluorescein-labeled peanut agglutinin to delineate the MCSA and rhodamine-labeled *Griffonia simplicifolia* lectin I to outline the capillaries. Four radially oriented microscope fields were selected from each section and photographed under the 40× objective. MCSA was measured by computer-based planimetry (Microsuite Biological Suite) and averaged across all four fields of the sections. To directly assess collagen deposition in the heart, we also performed picrosirius red staining on frozen sections. Photographs of five randomly chosen fields per section were taken under the ×20 objective, and the percentage of collagen staining per field was measured using Image J software. The mean percentage was then calculated for each animal. All assessments were performed by blinded observers.

**Real-time RT-PCR.** Real-time RT-PCR for prostacyclin synthase (PGIS), collagen type I, and collagen type III was performed by quantitative real-time RT-PCR using a SYBR green method. Predesigned mouse-specific primers from SA Biosciences (Frederick, MD) were used for all PCR reactions. Real-time RT-PCR was performed as follows: 1 μg of DNase-treated total RNA sample was reverse transcribed using random primers and Omniscript reverse transcriptase (Qiagen, Valencia, CA) in a total volume of 20 μl for 1 h at 37°C followed by an inactivation step of 95°C for 5 min. Two microfilters of the reverse transcription reaction were then amplified in a Roche version 2.0 lightcycler PCR instrument (Roche, Indianapolis, IN) using SYBR green dye (SA Biosciences) and specific primers. Reactions were set up in a final volume of 20 μl, which contained 2 μl of sample, 1 μM each of both the primers and 10 μl of 2× SYBR green PCR mix. After an initial "hot start" at 95°C for 10 min, amplification occurred by denaturation at 95°C for 15 s and then annealing/extension at 60°C for 1 min for a total of 30–40 cycles. At the end of PCR cycling, melting curve analyses were performed, and representative PCR products were run on agarose gels and visualized by ethidium bromide staining. A relative quantitation method (ΔΔCt) (29) was used to evaluate expression of each gene relative to control. RT-PCR of GAPDH was used for normalization of all data.

**Measurement of cardiac prostanoids.** To measure cardiac prostanoids, mice were anesthetized with pentobarbital sodium, and their hearts were removed. The hearts were washed briefly in ice-cold PBS, the atria and right ventricle were removed, and the left ventricle with attached septum was snap-frozen in liquid N2. After storage at −80°C, the entire left ventricle plus septum was homogenized in 1 ml of methanol containing 10 μg/ml indomethacin. The volume of methanol was adjusted to 4 ml, and the tube was subjected to repeated vortexing over a 30-min period. After centrifugation at 1,500 g for 10 min at 4°C, the supernatant was dried overnight in a Savant and then reconstituted in 0.1 M phosphate buffer. One-half of this sample was then frozen at −80°C for determination of 6-keto-PGF₁α, PGE₂, and LTD₄.

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**Fig. 1.** Effect of microsomal (m) PGE₂ synthase (PGES-1) deletion on ANG II-induced hypertension. Values represent means ± SE. C57Bl/6 and mPGES-1 knockout (KO) mice were infused with either vehicle (Veh) or 1.4 mg·kg⁻¹·day⁻¹ ANG II. Systolic blood pressure (SBP) was measured at baseline (preinfusion, B) and over the 8-wk time course using the tail cuff method; n = 15–17 mice/group.

<table>
<thead>
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<th>Parameter</th>
<th>Vehicle</th>
<th>ANG II</th>
<th>P</th>
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<tbody>
<tr>
<td>Body wt, g</td>
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<td>29.2 ± 0.6</td>
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<td>EF, %</td>
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<td>Mass/body wt, mg/g</td>
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<td>2.76 ± 0.13*</td>
<td>0.001</td>
</tr>
<tr>
<td>CO, ml·min⁻¹·g body wt⁻¹</td>
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<td>0.75 ± 0.04</td>
<td>0.99</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>689 ± 6</td>
<td>687 ± 11</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Table 1. Mean echocardiography data**

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**Echocardiography data in C57Bl/6 and microsomal prostaglandin E synthase (mPGES-1) knockout (KO) mice after 8 wk infusion with either vehicle or 1.4 mg·kg⁻¹·day⁻¹ ANG II. Values are means ± SE; n = 14–16 mice/group. EF, ejection fraction; LVAd, left ventricular area at diastole; LVAs, left ventricular area at systole; Mass/body wt, mass-to-body weight ratio; CO, cardiac output; HR, heart rate. Statistical significance: *P < 0.05 and **P < 0.005 compared with respective vehicle control. +P < 0.005 compared with C57Bl/6 vehicle control.
thromboxane B₂ (TxB₂), and the other one-half was purified through PGE₂ affinity columns according to the manufacturer’s instructions (Cayman Chemicals, Ann Arbor, MI). After the sample was eluted from the column, the sample was dried in a Savant and then resuspended in 0.4 ml assay buffer. We have previously shown that this method of extraction results in >95% recovery of PGE₂, PGE₂, 6-keto-PGF₁α, PGF₂α, and TxB₂ were determined with enzyme-linked immunoassay kits from Cayman Chemicals according to the manufacturer’s protocol. Results were recorded as picograms per milligram of left ventricle.

**Western blot.** Mouse hearts were homogenized in sample buffer (in mmol/l: 25 Tris·HCl, 0.5 EDTA, and 0.5 EGTA (pH 7.5)) containing a proteinase and phosphatase inhibitor mixture (Roche). A total of 40 μg of protein per sample was electrophoresed and transferred to a polyvinylidene fluoride membrane. gp91phox (NOX2) protein was detected with an antibody from BD Biosciences (Franklin Lakes, NJ).

![Representative M-mode echocardiography on conscious animals from each of the 4 experimental groups at the end of the 8-wk study.](image)

Bar graphs show mean data for the effect of mPGES-1 deletion on left ventricular dimension at systole (LVDs, B), left ventricular dimension at diastole (LVDd, C), shortening fraction (SF, D), and posterior wall thickness at diastole (PWTd, E). Values represent means ± SE. C57Bl/6 and mPGES-1 KO mice were infused with either vehicle or 1.4 mg·kg⁻¹·day⁻¹ ANG II for 8 wk; n = 14–16 mice/group. Statistical significance: *P < 0.05 and ***P < 0.005 compared with respective vehicle control and +P < 0.05 for C57BL/6 vehicle vs. mPGES-1 KO vehicle group.
and used at a dilution of 1:1,000. The antibody-antigen reaction was detected using a secondary antibody linked to horseradish peroxidase. The protein bands were scanned, quantified, and reprobed with an antibody to GAPDH as a loading control. Values in C57Bl/6 mice were set to an arbitrary value of 1.00, and ratios between different groups were compared.

TdT-dUTP nick end labeling staining as an index of apoptosis. Frozen sections were fixed in 2% paraformaldehyde at room temperature for 30 min then washed three times with PBS for 5 min each wash. Afterward, TdT-dUTP nick end labeling (TUNEL) staining was performed using the TUNEL apoptosis detection kit (Millipore, Temecula, CA) according to the manufacturer’s instructions. Five randomly selected fields were photographed under fluorescence using the ×20 objective, and the number of positive cells was counted by a different investigator. All personnel were blinded to the experimental groups.

RESULTS

Effect of mPGES-1 deletion on blood pressure. At baseline, there was no difference in systolic blood pressure between mPGES-1 KO mice and C57BL/6 controls (105.7 ± 1.7 vs. 108.8 ± 1.8 mmHg, n = 15–17 mice/group). Blood pressure increased rapidly after 1 wk of ANG II infusion and then appeared to plateau during subsequent weeks (Fig. 1). Similar levels of systolic blood pressure were achieved in both strains after 8 wk of ANG II infusion (162.6 ± 2.6 mmHg for C57BL/6 vs. 156.5 ± 3.2 mmHg for mPGES-1 KO). No changes in blood pressure were noted after infusion with vehicle for 8 wk. Moreover, statistical analyses revealed no differences between strains in their responsiveness to ANG II. Thus any changes in cardiac function noted between the strains in response to ANG II cannot be ascribed to alterations in blood pressure.

Cardiac function in response to ANG II infusion. Table 1 shows echocardiographic analysis for both C57BL/6 control mice and mPGES-1 KO mice in response to an 8-wk infusion with either vehicle or 1.4 mg·kg⁻¹·day⁻¹ ANG II. In control mice, infusion of ANG II for 8 wk did not affect ejection fraction, and the left ventricular dimension was unchanged. In contrast, the infusion of ANG II to mice lacking mPGES-1 caused a significant decline in both ejection fraction and shortening fraction with left ventricle chamber dilatation at both systole and diastole (Fig. 2).

Infusion of ANG II increased the left ventricle (LV)-to-body weight ratio, mass-to-body weight ratio (as measured by echo), and MCSA to a similar extent in both strains (Fig. 3), consistent with the similar elevations in systolic blood pressure. However, posterior wall thickness increased by an average of 0.22 mm in control mice, whereas it only increased by 0.14 mm in KO mice (P = 0.054), suggesting an impaired hypertrophic response.

Although systolic blood pressure was not different between strains, heart rate was significantly increased in vehicle-infused mPGES-1 KO mice compared with vehicle-infused controls (729 ± 7 vs. 689 ± 6 beats/min, P < 0.001), an effect that was apparent in young animals even before infusion (718 ± 3 beats/min in KO mice vs. 693 ± 5 beats/min in age-matched controls, P < 0.001). Neither C57Bl/6 nor mPGES-1 KO exhibited any significant change in heart rate after 8 wk of ANG II infusion.

MCSA and picrosirius red estimation of collagen. Figure 3 shows that MCSA was not different between C57BL/6 and mPGES-1 KO mice infused with vehicle for 8 wk (126.9 ± 1.8 vs. 131.4 ± 2.2 μm²), consistent with the LV-to-body weight ratios. As expected, ANG II infusion increased MCSA in control animals, and a similar increase was observed for mPGES-1 KO mice. Measurements of picrosirius red to directly assess collagen showed that infusion of ANG II increased fibrosis, but there was no difference between the strains in their responsiveness (Fig. 4). These data were confirmed by real-time RT-PCR data showing that both collagen type I and type III mRNA were increased after ANG II infusion but that the magnitude of this response did not differ between strains (Fig. 5).

Real-time RT-PCR for PGIS mRNA. To determine whether knockout of mPGES-1 results in a redirection of prostanooid synthesis, we measured PGIS by real-time RT-PCR. Expression of PGIS in the left ventricle was similar in both strains infused with vehicle and was increased equally by infusion of mPGES-1 KO mice.
ANG II (Fig. 6). In C57Bl/6 mice infused with vehicle, expression of PGIS corrected to GAPDH was 1.03 ± 0.09 arbitrary units and was 1.38 ± 0.12 arbitrary units in mice infused with ANG II \((P < 0.05, n = 7)\). Likewise, in mPGES-1 KO mice, expression of PGIS corrected to GAPDH was 0.86 ± 0.23 arbitrary units and was 1.39 ± 0.17 arbitrary units in mice infused with ANG II \((P = 0.09, n = 7)\). These results suggest that genetic deletion of mPGES-1 does not result in enhanced prostacyclin production.

**Cardiac prostanoid production.** To determine whether cardiac prostanoids are altered in response to genetic deletion of mPGES-1, we measured PGE2, 6-keto-PGF\(_{1\alpha}\) (stable metabolite of PGI2), PGF\(_{2\alpha}\), and TxB\(_2\) (stable metabolite of TxA\(_2\)) in portions of left ventricle (Table 2). In agreement with the PGIS real-time RT-PCR data, genetic deletion of mPGES-1 did not enhance cardiac PGI2 production. Likewise, PGE2 production was not different between C57Bl/6 and mPGES-1 KO mice treated with vehicle. In contrast, both PGF\(_{2\alpha}\) and TxA\(_2\) tended to be reduced in left ventricles of mPGES-1 KO mice compared with C57Bl/6 mice, although these differences did not achieve statistical significance \((P = 0.066 \text{ and } P = 0.10, \text{ respectively})\). Furthermore, chronic infusion of ANG II significantly reduced both PGI2 and PGF\(_{2\alpha}\) in control C57Bl/6 mice but was without effect on PGE2. TxA\(_2\) was below the limits of detection in both groups of mPGES-1 KO mice. Additionally, infusion of ANG II had no effect on the other cardiac prostanoids from left ventricles of mPGES-1 KO mice.

**gp91phox (NOX2) expression as an index of oxidative stress.** ANG II is well known to cause oxidative stress to elicit some of its deleterious effects. To determine whether oxidative stress differed between strains after ANG II infusion, we measured expression of gp91phox (NOX2) by Western blot in left ventricle samples and corrected to GAPDH as a loading control (Fig. 7). gp91phox (NOX2) is a membrane-bound subunit of NAD(P)H oxidase that generates superoxide, and the mouse form is detected as a doublet at both 54 and 58 kDa instead of the 91-kDa band seen in humans (BD Transduction Laboratories Data Sheet). An 8-wk infusion of ANG II increased expression
mPGES-1 KO (receiving ANG II) and from 5.88 to 11.6% in mPGES-1 KO mice receiving vehicle compared with respective vehicle control and +P < 0.05 for C57Bl/6 vehicle vs. mPGES-1 KO vehicle group.

The results of this study indicate that mPGES-1 plays a key role in maintaining cardiac function in ANG II-dependent hypertension that its gene deletion reduces ejection fraction and results in left ventricle chamber dilatation after ANG II infusion.

COX-2 and its product PGE2 are induced in the ischemic heart, contributing to inflammatory cell infiltration, fibroblast proliferation, and cardiac hypertrophy (18, 24). Previous studies from this laboratory indicate that mPGES-1 is induced in the rodent heart after MI and ANG II infusion. In addition to infarction and heart failure, COX-2 and mPGES-1 are elevated in atherosclerotic plaques, contributing to instability and rupture (1, 1, 7).

A major role for mPGES-1 in inflammation has been identified using KO mice. Initial characterizations indicated that mPGES-1 was necessary for lipopolysaccharide (LPS)-stimulated PGE2 production by macrophages (27) and also involved in acute pain hypersensitivity, inflammation, and the pathogenesis of rheumatoid arthritis (15, 17, 28). These studies also indicated that mPGES-1 was constitutively expressed only in a limited number of tissues, including the kidney and stomach. Otherwise, tissue levels of PGE2 were equivalent in KO and wild-type mice. Studies using mPGES-1 KO mice on a C57Bl/6 × 129/SVJ background showed no differences in other PGE2 synthetic enzymes (cPGES and mPGES-2), COX-1 and COX-2 and prostanoids produced by LPS-stimulated macrophages vs. wild-type controls (15). In contrast, when mPGES-1 KO mice were produced on a different background (DBA/1LacJ), LPS-stimulated macrophages produced more TxA2 and PGI2 than wild-type counterparts, indicating that eicosanoid metabolism could be redirected, at least in this cell type (27). Whole animal studies recently showed that the

by only 24% in C57Bl/6 mice (P = not significant) but by 116% in mPGES-1 KO mice (P = 0.06). Thus these results suggest that mPGES-1 KO mice demonstrate increased oxidative stress in response to ANG II.

TUNEL staining as an index of apoptosis. The amount of TUNEL staining positivity (Fig. 8) was significantly increased in mPGES-1 KO mice receiving vehicle compared with C57Bl/6 controls (5.88 ± 0.66 vs. 3.61 ± 0.59, respectively, P < 0.05). Infusion of ANG II for 8 wk increased the amount of apoptosis in both strains. The number of positive cells increased from 3.61 ± 0.59 to 6.67 ± 0.79 in control mice receiving ANG II and from 5.88 ± 0.66 to 10.46 ± 1.34 in mPGES-1 KO (P < 0.005 for both strains).

DISCUSSION

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Table 2. Cardiac prostanoids

<table>
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<tr>
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<th>mPGES-1 KO</th>
<th>ANG II</th>
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<td>PGE2</td>
<td>0.93 ± 0.09</td>
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<tr>
<td>PGF2b</td>
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<td>0.64 ± 0.12*</td>
<td>0.80 ± 0.11</td>
<td>0.78 ± 0.16</td>
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</table>

Values are means ± SE. PGE2, 6-keto PGF1a, PGF2b, and TxB2 were determined with enzyme-linked immunoassay kits from Cayman Chemicals according to the manufacturer’s protocol. 6-keto PGF1a, PGF2b, and TxB2 were measured from nonextracted homogenates of left ventricle, whereas PGE2 was extracted using a PGE2 affinity column. Results were recorded as pg/mg of left ventricle. ND, not detectable at a limit of 7.8 pg/ml for the assay. Statistical significance: *P < 0.05 compared with respective vehicle control.
blood pressure, but cardiac function was well-compensated and remained virtually unchanged. In contrast, infusion of ANG II to mPGES-1 KO mice resulted in deterioration of cardiac function despite similar changes in blood pressure. The results from this study showing left ventricle chamber dilatation and reduced ejection fraction are also concordant with our recent findings that the absence of EP4 specifically in cardiomyocytes leads to dilated cardiomyopathy in aged male mice (8). Although both C57Bl/6 and mPGES-1 KO mice exhibited a similar increase in the LV-to-body weight ratio after ANG II infusion, our results indicate that the remodeling process differs between the two. The mPGES-1 KO mice exhibit chamber dilatation that contributes to increased left ventricular mass as determined by echo, whereas thickening of the left ventricle wall appears to be dominant in control mice. These results are consistent with our previous studies showing that PGE2 via its EP4 receptor causes cardiomyocyte hypertrophy (9, 21) and those of Streicher et al. (26) who demonstrated that cardiomyocyte-specific overexpression of COX-2 causes hypertrophy and fetal gene reactivation. Although the LV-to-body weight ratio increased similarly in both strains after ANG II infusion, the change in posterior wall thickness at diastole was less in KO mice than controls. Although these results may appear to be discordant, the differences in posterior wall thickness at diastole are probably too small to be accurately determined by weighing of the left ventricle. Also, the fact that MCSA was not different between strains might be explained by alterations in the length but not the width of myocytes, a parameter that was not evaluated in this study.

The reasons why ANG II infusion leads to diminished cardiac function in mPGES-1 KO mice but not C57Bl/6 mice are not clear. We have attempted to examine signaling molecules in these hearts but were not able to detect differences, perhaps due to the fact that peak expression is transient and our 8-wk study missed any earlier changes. Our data show that the mPGES-1 KO mice infused with vehicle already have a small but significant increase in left ventricle chamber dimension compared with C57Bl/6 mice receiving vehicle, which suggests that wall stress is elevated and that these animals are therefore predisposed to a decline in cardiac function after stress. This change in chamber dimension was not apparent in our baseline echo measurements performed when mice were younger (10–12 wk old) but was evident at the conclusion of the study, indicating that the change developed with advancing age.

The observation that mPGES-1 KO mice have a higher heart rate than their controls even during preinfusion measurements is suggestive of increased sympathetic activity in this strain although we did not measure plasma norepinephrine levels to confirm this possibility. Increased sympathetic activity has been related to increased oxidative stress in models of renovascular hypertension (22) and in brains of animals with salt-sensitive hypertension (5) but whether this occurs in mPGES-1 KO mice requires further study. Jia et al. (14) recently reported that mPGES-1 KO mice exhibit increased renal vascular resistance after an acute infusion of ANG II that correlated with increased mean arterial pressure in these animals. The authors suggested that the absence of mPGES-1 exposes the mice to greater oxidative stress in the vasculature after ANG II infusion and that it is the antioxidant properties of PGE2 that are responsible for its protective effect. A subsequent study by the same group (13) also showed that the
absence of mPGES-1 exacerbated DOCA-salt hypertension together with increased oxidative stress and decreased nitric oxide and cGMP production. Recently published data by Zhang et al. (31) also provided evidence that mesenteric arteries from mPGES-1 KO mice show an enhanced pressor response to acute ex vivo treatment with ANG II. Thus it would appear that the antioxidant and vasodilator properties of PGE2 serve to offset the increased oxidative stress and vasoconstrictor effects of ANG II. Our data suggesting higher NOX2 in left ventricles of mPGES-1 KO mice after ANG II infusion would support this idea. Contrasting with papers showing that mPGES-1 may be beneficial, Wu et al. (30) reported that inhibition of COX-2 but not gene deletion of mPGES-1 is deleterious in a model of cardiac ischemia. However, most studies support a protective role for mPGES-1.

Our data also show that the absence of mPGES-1 enhances apoptosis in response to chronic ANG II infusion and, furthermore, that the degree of apoptosis is already enhanced in the hearts of mPGES-1 KO mice under basal conditions (vehicle infusion), which would point to an antiapoptotic effect of PGE2. The literature provides evidence for both anti- and proapoptotic effects of PGE2. Using cultured neonatal rat ventricular myocytes, Frias et al. (4) reported that PGE2 inhibits doxorubicin-induced DNA fragmentation via Stat 3 and p42/44 mitogen-activated protein kinase (4), whereas Hickson-Bick et al. (10) showed opposite effects in the same cell type. These conflicting effects of PGE2 have also been noted in other cell types (11, 19, 20).

In conclusion, our data support the evidence that gene deletion of mPGES-1 has a deleterious effect on cardiac function after stress with ANG II. Overall, our results are consistent with a beneficial effect of mPGES-1 in the maintenance of cardiac function in ANG II-dependent hypertension. These results therefore suggest that inhibition of mPGES-1 may not be a useful clinical strategy as an alternative to COX-2 inhibitors.

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