Prostaglandin E2 Reduces Cardiac Contractility via EP3 Receptor

Xiaosong Gu, MD, PhD; Jiang Xu, MD; Liping Zhu, PhD; Timothy Bryson, BS; Xiao-Ping Yang, MD; Edward Peterson, PhD; Pamela Harding, PhD

Background—Prostaglandin E2 (PGE₂) EP receptors EP3 and EP4 signal via decreased and increased cAMP production, respectively. Previously, we reported that cardiomyocyte-specific EP4 knockout mice develop dilated cardiomyopathy with reduced ejection fraction. Thus, we hypothesized that PGE₂ increases contractility via EP4 but decreases contractility via EP3.

Methods and Results—The effects of PGE₂ and the EP1/EP3 agonist sulprostone on contractility were examined in the mouse Langendorff preparation and in adult mouse cardiomyocytes. Isolated hearts of adult male C57Bl/6 mice were perfused with PGE₂ (10⁻⁶ M) or sulprostone (10⁻⁶ M) and compared with vehicle. Both PGE₂ and sulprostone decreased +dp/dt (P<0.01) and left ventricular developed pressure (P<0.001) with reversal by an EP3 antagonist. In contrast, the EP4 agonist had the opposite effect. Adult mouse cardiomyocytes contractility was also reduced after treatment with either PGE₂ or sulprostone for 10 minutes. We then examined the acute effects of PGE₂, sulprostone, and the EP4 agonist on expression of phosphorylated phospholamban and sarcoplasmic reticulum Ca²⁺-ATPase 2a in adult mouse cardiomyocytes using Western blot. Treatment with either PGE₂ or sulprostone decreased expression of phosphorylated phospholamban corrected to total phospholamban, whereas treatment with the EP4 agonist had the opposite effect. Sarcoplasmic reticulum Ca²⁺-ATPase 2a expression was unaffected. Finally, we examined the effect of these compounds in vivo using pressure–volume loops. Both PGE₂ and sulprostone decreased +dp/dt, whereas the EP4 agonist increased +dp/dt.

Conclusions—Contractility is reduced via the EP3 receptor but increased via EP4. These effects may be mediated through changes in phospholamban phosphorylation and have relevance to detrimental effects of inflammation. (Circ Heart Fail. 2016;9:e003291. DOI: 10.1161/CIRCHEARTFAILURE.116.003291.)

Key Words: cardiomyopathy, dilated ▪ heart contractility ▪ inflammation ▪ phospholamban ▪ prostaglandin E2

Prostaglandin E2 (PGE₂) elicits biological effects through 4 distinct receptor subtypes termed EP1, EP2, EP3, and EP4 that couple to different second messenger systems. Whereas activation of EP2 and EP4 increases cAMP, activation of EP1 increases intracellular calcium and activation of EP3 decreases cAMP. Thus, the effect of PGE₂ is dependent on the profile of EP receptors expressed in different tissues and cell types.

See Clinical Perspective

Our laboratory recently reported that male mice lacking the EP4 receptor subtype only in cardiac myocytes (EP4 knockout) have reduced cardiac function with age and develop a phenotype of dilated cardiomyopathy.¹ However, these in vivo studies could not discern whether the EP4 knockout mice have intrinsic defects in myocyte contractility or whether decreased cardiac function results from whole system abnormalities in the sympathetic nervous system that regulates both the speed and force of contraction or whether these mice have conduction defects. Moreover, although we reported that EP3 mRNA is not increased in the heart of EP4 knockout mice to compensate for lack of EP4,² we now suggest that the absence of EP4 allows the effects of EP3 stimulation to proceed unopposed. There are few studies that have reported on the influence of PGE₂ on isolated myocyte contractility and the EP receptor(s) involved. Wang et al³ showed that cardiomyocyte-specific deletion of cyclooxygenase-2 increased ventricular tachycardia in response to electric stimulation of the heart and infusion of PGE₂, was reported to depress premature ventricular beats in humans, consistent with its ability to reduce ischemia-induced arrhythmias in animal models. There is only 1 published article describing the effect of PGE₂ on isolated rat myocytes in vitro, and it found that PGE₂ increased contractility without effects on intracellular calcium.⁴ However, these few reports do not allude to potential mechanisms by which PGE₂ increases the rate or force of contractions, including which PGE₂ receptor subtype is involved.
Phospholamban is a crucial component of excitation–contraction coupling. The phosphorylation of phospholamban (p-PLN) physically separates it from sarcoplasmic reticulum Ca\(^{2+}\)-ATPase 2a (SERCA2a) and, therefore, removes its inhibitory effect, making for increased SERCA activity and triggering the release of large amounts of Ca\(^{2+}\) from the sarcoplasim reticulum to increase contractility. Therefore, we tested the ability of PGE, and various EP agonists to alter contraction and examined the hypothesis that PGE, acting through its EP4 receptor can increase contraction via increased p-PLN, whereas PGE, acting through its EP3 receptor has the opposite effect. This hypothesis was tested in isolated mouse ventricular myocytes, in the ex vivo mouse working heart Langendorff preparation and acutely in vivo using pressure–volume (PV) loops.

Methods

Animal Use

The wild-type and EP4 knockout mice used in this study were bred and genotyped at Henry Ford Hospital and have been previously described.\(^1\) C57Bl/6 mice used for the myocardial infarction (MI) studies and contractility studies were from Jackson laboratories. The mouse model of MI using permanent ligation of the left anterior descending coronary artery was previously described by ries. The MI studies and contractility studies were from Jackson laborato-

Chemicals

The EP1/EP3 agonist (sulprostone), EP4 agonist (CAY 10598), and EP4 antagonist [L798106] were obtained from Cayman Chemical (Ann Arbor, MI). All drugs were dissolved in 100% ethanol. All other chemicals were obtained from Sigma Aldrich.

Mouse Langendorff Studies

Mice were anesthetized with isoflurane and injected with 250 U heparin. Hearts were rapidly excised and placed in ice-cold Krebs solution (mmol/L: NaCl 118.5, KCl 4.7, MgSO\(_4\) 2.46, KH\(_2\)PO\(_4\) 1.21, glucose 12, CaCl\(_2\) 1.7, Na pyruvate 2, NaHCO\(_3\) 25, pH 7.4, bubbled in 95% O\(_2\)/5% CO\(_2\)). The aortas were cannulated and retrogradely perfused using an in-line pressure transducer (MLT0380/D; ADInstruments, Australia). After 10-minute equilibration, chemicals or vehicle was added to the buffer and perfusion was continued for 30 minutes. Left ventricular (LV) end-diastolic pressure, LV end-systolic pressure, and heart rate were monitored and recorded continuously using PowerLab system (ADInstruments). LV developed pressure (LVDP) was calcu-

Isolation of Adult Cardiomyocytes for Contractility Studies

Isolation of cardiomyocytes from 16- to 21-week-old C57Bl/6 male mice was performed using modifications of the method described by O’Connell et al\(^7\) and has previously been described by us.\(^2\) 2,3-butanediol monoxide (10 mmol/L) was omitted as it is a known inhibitor of contractility. Freshly isolated A VM were prepared in Tyrode solution loaded with 1 µmol/L Fura-2 AM (Molecular Probes, Eugene, OR) for 5 minutes at room temperature, washed, and rested for 15 minutes. After cells were loaded and rested, cardiomyocytes were di-

Effect of PGE2 and Sulprostone on A VM

Cell Culture and Western Blot

Phospholamban and p-PLN protein expression was measured by Western blot in AVM treated with PGE\(_2\), CAY 10598, and sulprostone for various times. For the cell culture studies to investigate the effect of PGE, and EP agonists on phospholamban and p-PLN expression, we used primary cultures of AVM from 18- to 20-week-old C57Bl/6 male mice. Cells were plated, and after 1 hour the media was changed to serum-minus media. After an additional hour, the cells were treated and cell lysates were harvested at appropriate times.

Western blot analysis was performed under reducing conditions using 20 µg of total protein. After electrophoresis, proteins were trans-

Statistical Analysis

All statistics were performed by a statistician in the Department of Public Health Sciences of Henry Ford Hospital using the statistical package SAS version 9.4. For the contractility data, statistics are re-

Results

Effect of PGE2 and Sulprostone on AVM Contractility

The top panel of Figure 1A shows mean data of transients from cells treated with vehicle and cells treated with PGE\(_2\),
The bottom panel of the same figure shows mean transients from cells treated with vehicle and cells treated with sulprostone. Treatment with PGE₂ (10⁻⁶ M) for 10 minutes reduced contractility as measured by peak height (6.84±0.7 for vehicle versus 3.85±0.3 for PGE₂; *P<0.001), departure velocity (−250.0±25.2 μm/s for vehicle versus −142.2±11.2 μm/s for PGE₂; *P<0.001), and return velocity (147.9±19.3 μm/s for vehicle versus 65.8±8.6 μm/s for PGE₂; *P<0.001).

Under basal conditions, treatment of AVM for 10 minutes with 10⁻⁶ M sulprostone also reduced contractility as measured by peak height (7.41±0.4 for vehicle versus 4.44±0.43 for sulprostone; *P<0.001), departure velocity (−281.3±15.7 μm/s for vehicle versus −194.6±19.0 μm/s for sulprostone; *P<0.001), and return velocity (178.8±12.8 μm/s for vehicle versus 120.4±15.3 μm/s for sulprostone; *P=0.008). The mean data for the effects of PGE₂ and sulprostone are presented in Figure 1B.

With regard to changes in intracellular calcium, treatment with 10⁻⁶ M PGE₂ increased sin exp tau (the exponential decay time constant for calcium) from a value of 0.082±0.003 in vehicle-treated cells to 0.094±0.004 in PGE₂-treated cells, *P=0.008. Treatment with sulprostone did not significantly increase this parameter. These results indicate a slower return to baseline calcium levels in cells treated with PGE₂.
Effect of PGE2, Sulprostone, and EP4 Agonist (CAY 10598) on Contractility of the Isolated Heart

Isolated hearts of 18- to 20-week-old male C57Bl/6 mice were mounted on the Langendorff apparatus, equilibrated for 10 minutes, and then perfused with PGE2 (10−6 M) or sulprostone (10−6 M) for 30 minutes. Values at the end of equilibration were set to 100%. Compared with vehicle, PGE2 decreased +dp/dt (77.8±3% for PGE2 versus 96.7±3% for vehicle; \(P=0.004\)) and LVDP (77.2±2% versus 96.8±3%; \(P<0.001\)). Sulprostone decreased +dp/dt (75.9±2% versus 96.7±3%; \(P<0.001\), −dp/dt (72.2±1% versus 85.7±1%; \(P=0.01\)) and LVDP (70.9±1% versus 96.8±3%; \(P<0.001\)). The effects of both PGE2 and sulprostone were reversed by the EP3 antagonist, L789106 (10−6 M). In contrast to the effect of sulprostone and PGE2, perfusion of the EP4 agonist into isolated working hearts increased their contractility. Compared with vehicle, the EP4 agonist, CAY 10598 (10−6 M) increased +dp/dt (117±9% versus 97±7%; \(P=0.006\)), −dp/dt (105±8% versus 86±3%; \(P=0.006\)), and LVDP (112±7% versus 97±8%; \(P=0.007\); n=5 mice). To confirm specificity of the EP4 agonist, we then performed experiments to determine the effect of the EP4 agonist in working hearts from EP4 knockout mice in which the EP4 receptor is deleted only in cardiac myocytes. As anticipated, the EP4 agonist had no effect on contractility of hearts obtained from these knockout animals (Figure 2).

Effect of PGE2, Sulprostone, and EP4 Agonist In Vivo

The acute in vivo effects of the above compounds were determined using PV loops in a closed chest approach. Similar to the results observed in the isolated adult myocytes and Langendorff preparation, both PGE2 and sulprostone decreased contractility when compared with baseline measurements. In contrast, acute treatment with the EP4 agonist significantly improved contractility as measured by increased +dp/dt and heart rate. These results are presented in the Table and Figure 3.

Effect of PGE2, Sulprostone, and EP4 Agonist (CAY 10598) on p-PLN and SERCA2a Expression

Treatment of AVM for 15 minutes with either PGE2 or sulprostone decreased the expression of p-PLN corrected to total phospholamban, by 67% and 43%. SERCA2a expression was unaffected (data not shown), which was anticipated in this short experimental time frame. In contrast, treatment with the EP4 agonist increased p-PLN corrected to total phospholamban by 3.7±0.6-fold, \(P=0.005\), n=3 separate preparations. To further explore the role for the EP receptors in p-PLN, we examined AVM from 13- to 15-week-old male EP4 knockout mice. In these mice, treatment with PGE2, for 15 minutes reduced p-PLN/total phospholamban by an average of 81%, a value that appeared greater than the 67% reduction observed in C57Bl/6 mice.
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Table. Effect of PGE$_2$, Sulprostone (EP1/EP3 Agonist), and CAY 10598 (EP4 Agonist) on Pressure–Volume Relationship in C57BL/6 Mice

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PGE$_2$</th>
<th>Sulprostone</th>
<th>CAY 10598</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base 30 min</td>
<td>Base 30 min</td>
<td>Base 30 min</td>
<td>Base 30 min</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>326.7±14.2</td>
<td>313.7±8.9</td>
<td>419.8±39.1</td>
<td>391.2±39.0*</td>
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<tr>
<td>SBP$_{end}$, mm Hg</td>
<td>85±2.5</td>
<td>85.3±1.9</td>
<td>87.2±11.0</td>
<td>80±6.5</td>
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<tr>
<td>DBP$_{end}$, mm Hg</td>
<td>5.8±0.8</td>
<td>5.7±1.0</td>
<td>2.8±1.4</td>
<td>3.4±1.3</td>
</tr>
<tr>
<td>ESV, µL</td>
<td>36.5±3.3</td>
<td>39±4.3</td>
<td>17±2.2</td>
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<tr>
<td>EDV, µL</td>
<td>61.3±6.5</td>
<td>62.5±6.8</td>
<td>36±4.1</td>
<td>30.6±5.1</td>
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<td>SV, µL</td>
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<td>21.5±2.8</td>
<td>17±3.6</td>
<td>10.8±2.7†</td>
</tr>
<tr>
<td>CO, µL/min</td>
<td>8065±1239</td>
<td>7823±1806</td>
<td>7588±971</td>
<td>4060±692*</td>
</tr>
<tr>
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<td>52.8±5.5</td>
<td>31.8±5.0†</td>
</tr>
<tr>
<td>+dp/dt, mm Hg/s</td>
<td>5109±316</td>
<td>5095±291</td>
<td>5385±769</td>
<td>4634±576*</td>
</tr>
<tr>
<td>−dp/dt, mm Hg/s</td>
<td>3721±279</td>
<td>3654±149</td>
<td>5063±732</td>
<td>4375±642*</td>
</tr>
</tbody>
</table>

Data represent mean±SEM of 4–6 male 18–20-week-old C57BL/6 mice. Pressure–volume loop parameters obtained in anesthetized mice using a closed chest approach. Data were obtained at baseline and after 30-min infusion with compounds. CO indicates cardiac output; +dp/dt and −dp/dt, maximum and minimum change in pressure with time respectively; DBP$_{end}$, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; PGE$_2$, Prostaglandin E2; SBP$_{end}$, end-systolic pressure; and SV, stroke volume.

Statistical significance: *P<0.05, †P<0.01, and ‡P<0.005 by paired t test vs baseline values.

with the EP3 antagonist in AVM from EP4 knockout mice prevented the ability of PGE$_2$, to reduce p-PLN/total phospholamban (Figure 4B).

EP3 and EP4 Are Increased in the MI Heart

To determine whether the expression of EP3 and EP4 is altered in the failing heart, we performed real-time reverse transcription

Figure 3. Representative left ventricular pressure–volume loops obtained from closed chest preparations in C57Bl/6 mice. Green loop is baseline and blue loops are loops obtained after 30-min treatment with compounds (30 µg/kg per min).
polymerase chain reaction on LV samples from hearts obtained from C57Bl/6 mice that were subjected to permanent ligation of the LAD for 2 weeks. All samples were obtained from the border-remote zone and not the infarcted section. Our data show that EP3 is increased 3.37±0.8-fold in the MI heart compared with sham-operated controls (P=0.016), and EP4 mRNA is also increased in those same hearts although to a lesser extent (2.12±0.35-fold; P=0.007).

Discussion

This study provides direct evidence that exogenous PGE₂ reduces contractility of the in vivo heart, the isolated working heart, and single adult ventricular myocytes via its EP3 receptor subtype, whereas stimulation of the EP4 receptor has opposite results. These effects may be mediated by alterations in the p-PLN, a protein that negatively regulates SERCA activity.

There have been many studies reporting the effect of PGE₂ on contractility, but the results have been conflicting and do not elucidate the contribution of the various receptor subtypes. Using the PGE₂-perfused mouse isolated heart, Liu et al⁸ reported that PGE₂ attenuates the adrenergic-induced cardiac contractile response in animal hearts, whereas studies by Pecha et al⁹ did not support a role for PGE₂ in regulating catecholamine-induced inotropy. Whether these differences relate to the different preparations used (isolated heart versus atrial and ventricular trabeculae) is not known. Moreover, Klein et al⁴ used a system similar to the one used in our studies to observe that PGE₂ augmented peak shortening in adult rat cardiomyocytes independent of changes in calcium, whereas concentrations >10⁻⁵ M reduced intracellular calcium. Church et al¹⁰ also reported that PGE₂ (10⁻⁵ M) increases the contraction frequency of neonatal rat cardiomyocytes, but only spontaneous beating was measured. Although our recent data conflict with those described above, our results across a spectrum of preparations ranging from isolated cardiomyocytes through the Langendorff preparation and in vivo using
PV loops are consistent and suggest that the main effect of PGE, via EP3 is to reduce contractility whereas it augments contractility via EP4. Our data are thus consistent with the reduced contractility noted in our previous studies using the cardiomyocyte-specific EP4 knockout mouse.

Clinical reports have also implicated the EP1/EP3 receptor agonist, sulprostone, in heart failure or cardiomyopathy. Vital et al. reported a case of a peripartum heart failure, whereas another case showed that sulprostone caused coronary spasm, bradycardia, and subsequent asystole. In EP3-overexpressing mice, LV ejection fraction was severely decreased in transgenic hearts whereas the relative LV mass was significantly increased. Using isolated rat atria, Wolkowicz et al. also reported that an EP1 agonist increased contractile force that was sensitive to Rho kinase inhibitors. In a Langendorff preparation, both endogenous PGE, and an exogenous EP4 agonist were shown to protect the heart from ischemia-reperfusion injury via EP4. These latter results are consistent with our findings that the EP4 agonist improves cardiac function in the same working heart preparation.

It is well established that PGE, signals through 4 receptors (EP1, EP2, EP3, and EP4) that signal via different mechanisms. In the mouse LV, expression of EP3 and EP4 mRNAs is higher than that of EP1 and EP2. Indeed, Xiao et al. were unable to detect EP1 in the mouse heart using quantitative PCR, whereas other literature supports its presence. The results in our present study provide direct evidence that exogenous PGE, can reduce contractility of both the isolated heart and isolated myocytes acutely via its EP3 receptor. We were rather surprised to note that the effect of PGE, mirrored that of the EP1/EP3 selective agonist sulprostone, despite the fact that the isolated heart and the isolated cardiac myocyte express EP4 receptors abundantly as measured by real-time reverse transcription polymerase chain reaction. Although the reason for this finding is not clear, one could speculate that either EP4 but not EP3 is rapidly internalized after agonist stimulation or that the receptors are compartmentalized differently. However, we have data (not shown) indicating that within a 1-hour time frame, AVM are able to increase cAMP production in response to repeated doses of either PGE, or the EP4 agonist, suggesting that the former may not be correct in cardiac myocytes. Further experiments are needed to examine these possibilities.

Because both cyclooxygenase-2 and microsomal PGE synthase-1 are upregulated in the infarcted heart to increase production of PGE, we were interested to examine whether the expression of EP3 and EP4 was also affected. Although our experiments were limited to studies of mRNA levels because of difficulties with the commercially available EP3 and EP4 antibodies, our data show that both EP3 and EP4 mRNAs are upregulated after MI although this is seemingly greater for EP3. We thus speculate that the altered balance between EP3 and EP4 in heart failure contributes to the diminished contractility observed in pathological conditions characterized by increased PGE.

Almost a decade ago, Schutte et al. reported that the administration of PGE, to sheep improved cardiac contractility and relaxation while decreasing heart rate. In contrast, however, similar administration to sheep in congestive heart failure reduced cardiac function with increased preload. These results lead the authors to speculate that PGE, might not be a suitable agent for treatment of congestive heart failure because of the worsening effect it had on the cardiodynamics of the failing heart. Our results suggest that administration of a selective EP4 agonist might be a more promising option. Indeed, the first clinical report was very recently published showing that an EP4 agonist had a lucistropic and vasodilator effect in healthy volunteers. This was followed by a concurrent publication showing that acute infusion of an EP4 agonist to normal anesthetized dogs increased ejection fraction and +dp/dt but decreased end systolic pressure. Our results add to evidence for a protective effect of EP4 but provide additional mechanistic insight.

Ca2+ is known to be important in myocyte contraction and relaxation. Selective stimulation of EP2 or EP4 receptors attenuates histamine-evoked Ca2(+)ATPase (SERCA2a) activity and cardiac contractility. Diphosphorylated phospholamban inhibits SERCA2a and phospholamban phosphorylation, at either Ser or Thr by protein kinase A or Thr by Ca(2+)calmodulin-dependent protein kinase, reverses this inhibition. Through this mechanism, phospholamban is a key modulator of sarcomplastic reticulum Ca(2+)uptake, Ca(2+)load, contractility, and relaxation. Previously, our gene array data on LV from EP4 knockout mice showed reduced phospholamban in knockout mice with the reduction correlating with ejection fraction (data submitted to the GEO database-NCBI). However, these data were obtained from older mice in various stages of heart failure and could not discern phosphorylation status. In support of our data, Liu et al. reported that PGE, inhibits adrenergic-induced p-PLN and the contractile response in animal hearts. However, they did not observe any effect under basal conditions and they implicated the EP4 receptor, whereas our results showing that PGE reduces p-PLN in isolated myocytes suggests that this is an EP3-mediated event, consistent with the Langendorff data.

In conclusion, our data clearly show that PGE, has an acute and direct effect on cardiac contractility; a positive inotropic effect mediated by its EP4 receptor and a negative inotropic effect mediated by its EP3 receptor. These effects were consistent in experiments ranging from isolated myocyte contractility studies through those in the intact animal. Our results have importance in situations where PGE, is elevated such as various inflammatory conditions and thus suggest a new deleterious relationship between inflammation and cardiac function that is mediated via the PGE2 EP3 receptor subtype.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Our laboratory previously reported that cardiomyocyte-specific EP4 knockout mice develop dilated cardiomyopathy with reduced ejection fraction. We thus hypothesized that prostaglandin E2 (PGE2) increases contractility via EP4 but decreases contractility via EP3. Our present study includes the influence of PGE2 and its receptor subtypes (EP1–4) on cardiac contractility using isolated mouse cardiomyocytes, the Langendorff heart preparation, and in vivo using pressure–volume loops in the anesthetized mouse. Our studies show that PGE2 has opposing effects on contractility dependent on which receptor subtype is activated. In general, contractility was reduced via the EP3 receptor but increased via EP4. In the working heart, both PGE2 and the EP1/EP3 agonist sulprostone decreased left ventricular developed pressure via EP3, whereas the EP4 agonist had the opposite effect. Single myocyte contractility was also reduced after treatment with PGE2, or sulprostone. The negative inotropic effects of PGE2 and the EP3 agonist seemed to be mediated by decreased phosphorylation of phospholamban without effects on SERCA2a expression. The in vitro hemodynamic effects of PGE2 and sulprostone were mimicked acutely in vivo using pressure–volume loops. Both PGE2 and sulprostone decreased +dp/dt, whereas the EP4 agonist increased +dp/dt. Our results may have potential clinical significance as we also observed increased EP3 expression in mice subject to myocardial infarction. If these results translate to the patient population, they suggest that blockade of the EP3 receptor could ameliorate worsening cardiac function observed in inflammatory conditions characterized by increased PGE2. Furthermore, they suggest a potentially protective role for EP4 agonists.
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