Hemodynamic effects of prostaglandin E₁ infusion in patients with acute myocardial infarction and left ventricular failure

Prostaglandin E₁ (PGE₁) has been shown to limit infarct size, improve coronary blood flow, inhibit platelet aggregation, and reduce both left ventricular (LV) preload and afterload in experimental animals. Its use in the therapy of patients with acute myocardial infarction (AMI) and congestive heart failure (CHF) has not, however, been reported. Five patients with AMI of less than 12 hours’ duration and LV dysfunction were studied to assess the hemodynamic effects of IV infusion of PGE₁. PGE₁ in the concentration of 0.4 μg/ml was infused at a rate of 0.003 μg/kg/min (3 ng · kg⁻¹ · min⁻¹) to a maximum rate of 0.021 μg/kg/min (21 ng · kg⁻¹ · min⁻¹) for a total time of up to 90 minutes. There was an insignificant increase in heart rate, with significant decreases in mean arterial blood pressure and systemic vascular resistance. Pulmonary capillary wedge pressure declined from 21 ± 3 to 15 ± 1 mm Hg (p < 0.05), mean pulmonary artery pressure and pulmonary vascular resistance decreased (p < 0.05), with increases in cardiac index from 2.38 ± 0.08 to 2.89 ± 0.58 L/min/m² (p < 0.01) and stroke volume from 51 ± 17 to 59 ± 20 ml/beat (p < 0.05). No major cardiac or extracardiac side effects were encountered during PGE₁ infusion. One patient had transient nausea which did not require discontinuation of the drug.

PGE₁ is an effective vasodilator and deserves further application in therapy for AMI patients with CHF. (Am Heart J 103:485, 1982.)


Prostaglandin E₁ (PGE₁) has been shown to improve coronary blood flow,¹⁴ reduce both left ventricular (LV) preload and afterload,²,³ decrease platelet aggregation,⁴ and limit infarct size in animals.⁷,⁸ Recent animal studies have shown that PGE₁ significantly reduces cardiac work and diminishes ST segment elevation during myocardial ischemia.⁹ Its use in therapy for patients with acute myocardial infarction (AMI) and LV dysfunction has not, however, been reported. In part, the lack of PGE₁ application in clinical AMI appears to be the result of concern about gastrointestinal or other distressing side effects. The purpose of the present patient study was to determine whether administration of PGE₁ could beneficially alter the hemodynamic disturbances associated with AMI without adverse side effects.

METHODS

Patient population. Five patients, including three men and two women ages 46 to 72 years (mean age, 64 years), with AMI of less than 12 hours’ duration and LV dysfunction, were studied. LV dysfunction was defined by the presence of bibasilar pulmonary rales and/or third heart sound and LV filling pressure (LVFP) of more than 15 mm Hg. Four patients had ECG evidence of anterior and one of inferior transmural AMI. The diagnosis of transmural infarction was based on ECG findings of acute ST segment elevation followed by development of pathologic Q waves or substantial decrease in R wave voltage, coincident with serum myocardial enzyme changes typical of AMI. Three patients were in Killip class II and two patients were in Killip class III. Conventional treatment, including sedation, oxygen, narcotics, and antiarrhythmic agents such as lidocaine, was prescribed when indicated but the administration of any vasodilators, diuretics, or other agents with known substantive hemodynamic effects was withheld until hemodynamic study of PGE₁ had been completed.

Hemodynamic determinations. The patients were admitted to the coronary care unit and informed consent was obtained. A 7F Lexington thermodilution catheter was positioned in the pulmonary artery (PA) via an antecubital vein cutdown and a short plastic catheter was inserted percutaneously into the radial artery. PA pressure and systemic arterial pressure (AP) were monitored simultaneously by use of Statham P231D and Bently 800 transducers, respectively. Cardiac output (CO) was measured by the thermodilution technique with the use of 10 ml of sterile normal saline at room temperature. Each CO recorded was the mean of at least two consecutive deter-
minations having the maximal variation of less than 10%.
The ECG lead with the greatest ST segment elevation was
monitored. Blood was drawn for routine hematologic and
blood chemistry studies before and during the PGE,
infusion. Control hemodynamic indices including heart
rate (HR), phasic and mean systemic AP, LVFP measured
as pulmonary capillary wedge pressure, phasic and mean
PA pressure, and CO were determined at least twice at
15-minute intervals before the infusion.

**PGE, infusion.** A solution of PGE, (Prestin VR, Upjohn
Co., Kalamazoo, Mich.) containing 0.4 µg/ml was prepared
with 5% dextrose. PGE, infusion, regulated by a Harvard
pump (Model 901), was begun in the central venous
circulation and the dose was slowly increased every 10 to
15 minutes. Intravenous infusion was increased to 1 to 70
ml/min at 10 minutes and to 3.50 ml/min at 20 to 30
minutes. The desirable hemodynamic effects were
achieved at dosage range of 10 to 19 ng·kg⁻¹·min⁻¹, with
the average effective dose of 14.6 ng·kg⁻¹·min⁻¹. The
infusion rate was modified if systolic AP fell by 20 mm Hg
or more, if HR increased more than 20 bpm, or if LVFP
fell below 15 mm Hg. Hemodynamic measurements were
recorded every 15 minutes for the total infusion time of 90
minutes and for a further 60 minutes after the infusion
had been discontinued.

**Hemodynamic-related indices calculated.** The following
indices were derived: SWI = SVI × (MSP - LVFP) × 1.36/100,
where SWI represents stroke work index (gm · m/m²), SVI is stroke volume index (ml/m²), and
MSP is mean systemic pressure (mm Hg). SVR = K
(mean aortic pressure)/systemic flow = 80 (AO)/CO, and
PVR = K (mean pulmonary pressure)/pulmonary
flow = 80 (FA)/CO, where SVR represents systemic vas-
cular resistance, PVR is total pulmonary vascular resis-
tance, AO is mean aortic pressure, and FA is mean
pulmonary pressure; K represents the conversion factor
from hybrid units of mm Hg · L⁻¹ · min⁻¹ to metric units
of dyn. · sec · cm⁻². PAR = (FA - LVFP × 80)/CO,
where PAR is pulmonary arteriolar resistance.

**Statistical analysis.** Statistical analysis was performed
by use of Student’s paired t test. Numerical values are
reported as mean ± SEM.

**RESULTS**

**Hemodynamic effects.** The results of control and
peak hemodynamic responses during the PGE, infu-
sion are shown in Table I. During PGE, infusion,
HR increased slightly but did not reach statistical
significance. However, there were significant
decreases in mean systemic arterial pressure (MAP)
and mean pulmonary pressure (MPP) (Fig. 1). In
addition, LVFP, SVR, PVR, and PAR were signifi-
cantly reduced by PGE, (Figs. 2 and 3), while stroke
volume (SV), cardiac index (CI), and SWI were
increased (Figs. 2 and 4). Following discontinuation
of PGE, infusion, all hemodynamic parameters in
four of the five patients returned to control values
within 30 to 60 minutes. At this point, patients were
reated with conventional vasodilators. In one
patient, the pulmonary capillary wedge pressure
remained normal for up to 2 hours.

**Anti-ischemic effects.** Three patients had complete
relief of their chest pain during PGE, infusion.
There were, however, no significant ST changes in
the monitored precordial lead.

**Side effects.** No major side effects were encoun-
tered during the PGE, infusion; in particular there
was no abdominal discomfort, vomiting, or diarrhea.
However, it should be pointed out that this was a
pilot study with only a short duration of infusion.
One patient had transient nausea but did not feel
this sufficient to discontinue study.

**DISCUSSION**

Beneficial hemodynamic effects of PGE, in AMI with
congestive heart failure (CHF) due to balanced systemic
to arteriovenous dilation. The present study demon-
strates that administration of PGE, to patients with
AMI complicated by CHF results in significant
hemodynamic improvement and relief of LV dys-
function without significant tachycardia or other
side effects. The lack of substantive untoward extra-
cardiac events such as nausea, vomiting, and diar-
rhea despite hemodynamic improvement may be
related to the relatively small doses of PGE, neces-
sary to reduce LVFP and SVR; thereby relieving
pulmonary congestion and improving pump output.
Although previous animal studies have not sug-
gested an effect of PGE, on venous capacitance, the
results of the present study demonstrate reduction

### Table I. Peak hemodynamic responses during PGE, infusion in AMI

<table>
<thead>
<tr>
<th></th>
<th>HR (bpm)</th>
<th>MAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>MPAP (mm Hg)</th>
<th>CI (L/min/m²)</th>
<th>SV (ml)</th>
<th>SVR (dyne · sec · cm⁻²)</th>
<th>PVR (dyne · sec · cm⁻²)</th>
<th>PAR (dyne · sec · cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>78 ± 18</td>
<td>101 ± 8</td>
<td>21 ± 3</td>
<td>27 ± 4</td>
<td>2.38 ± 0.08</td>
<td>51 ± 17</td>
<td>1710 ± 527</td>
<td>509 ± 124</td>
<td>123 ± 52</td>
</tr>
<tr>
<td>PGE</td>
<td>83 ± 18</td>
<td>92 ± 5</td>
<td>15 ± 1</td>
<td>21 ± 3</td>
<td>2.89 ± 0.38</td>
<td>58 ± 20</td>
<td>1373 ± 423</td>
<td>328 ± 80</td>
<td>89 ± 44</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM. PCW = pulmonary capillary wedge pressure; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; NS = not significant (p > 0.05).
of LVFP to normal with moderate decrease in SVR accompanied by only modest rises in SV and CI. Thus, the considerable reduction in LVFP suggests that in AMI patients with CHF, PGE₁ therapy results in systemic venorelaxation.

Potential anti-ischemic properties of PGE₁. Although the present study was designed to examine the acute hemodynamic actions of PGE₁, this agent is also known to have other effects that may be beneficial in myocardial ischemia. PGE₁ has been shown to preserve myocardial cells during ischemia and diminish autolytic processes as evidenced by decreased myocardial creatine kinase (CK) and cathepsin D release and by preservation of myocardial CK activity, indicating protection of cardiac cell integrity.⁷,¹¹ PGE₁ increases coronary blood flow and decreases coronary vascular resistance.¹¹ PGE₁ also protects against isoproterenol-induced myocardial injury as evidenced by significant reductions in ST segment elevation and plasma free fatty acid concentration.¹² In addition, PGE₁ inhibits norepinephrine release¹⁴ and the attendant increase in lipolysis, thereby limiting the deleterious myocardial oxygen wasting effect resulting from catecholamine rise during AMI. The coronary vasodilatory action of PGE₁ in conjunction with reduced LV preload might favorably redistribute myocardial perfusion toward the subendocardium, the area most critically compromised during acute ischemia. It is also possible that PGE₁ might increase collateral blood flow directly or by reducing LVFP. Of particular interest is PGE₁ inhibition of platelet aggregation,¹⁵ since recent studies have indicated increased platelet aggregation in AMI patients and a pathogenetic role of such platelet dysfunction in the infarction process.¹⁶-¹⁸

Potential advantages of PGE₁, compared to other vasodilators in AMI. The beneficial hemodynamic effects observed in the present study have also been observed with other vasodilators such as nitroprusside and nitroglycerin.¹⁹,²⁰ However, the use of nitroprusside in the presence of acute myocardial ischemia has been of concern to some workers, since animal studies have suggested that nitroprusside may adversely alter the distribution of myocardial blood flow during experimental infarction.²¹,²² Hence, an alternative means of acute afterload reduction appears useful. While not directly compared, the effects of PGE₁ in this study seem similar to the balanced systemic arterial and venous dilation caused by nitroprusside, as shown by the 16%
increase in SV and 29% reduction in LVFP produced by PGE\textsubscript{1}. Nitroglycerin exerts a beneficial hemodynamic effect in AMI patients without increasing ST segment elevation or adversely affecting distribution of myocardial perfusion.\textsuperscript{20} However, nitroglycerin does not possess some of the other potential salutary properties of PGE\textsubscript{1}, such as inhibition of catecholamine release and diminished platelet aggregation. While another prostaglandin, prostacyclin (PGI\textsubscript{2}), provides greater in vitro antiplatelet aggregation and more potent coronary vasodilation compared to PGE\textsubscript{1}, the use of PGI\textsubscript{2} in AMI patients with congestive heart failure appears limited due to marked PGI\textsubscript{2} induced systemic vasodilatation and hypotension.

**Conclusions.** Although the number of patients included in the present study was relatively small, the salutary hemodynamic results are significant. In view of our clinical observations and the experimental data of others suggesting additional beneficial actions of PGE\textsubscript{1}, this therapeutic agent deserves further evaluation in the management of patients with AMI and LV failure.

**REFERENCES**

17. Salky N, Dugdale M: Platelet aggregation in acute and
PGE₃ hemodynamic effects in AMI with CHF

Comparative hemodynamic effects of digoxin vs nitroprusside in conscious dogs with aortocaval fistula-induced chronic left ventricular volume overload and normal systolic performance

We compared the effects of IV digoxin (0.04 mg/kg) and nitroprusside (NP) (1.2 and 1.8 μg/kg/min) on left ventricular (LV) performance in six preinstrumented conscious dogs with chronic volume overload and congestive heart failure (CHF) produced by an aortocaval fistula. At 3 and 6 hours after digoxin administration (serum level, 3.5 ± 0.6 ng/ml), there were no changes in heart rate, LV systolic (LVSP) and end-diastolic (LVEDP) pressures, LV dimensions, LV dP/dt,,, or percent minor diameter shortening as compared to control values in the resting state, after beta blockade, or during phenylephrine infusion. By contrast, NP produced a significant reduction (p < 0.05) in LVEDP (16 ± 3 to 10 ± 3 mmHg) at the smaller dose which caused no change in mean aortic pressure. The larger dose of NP further reduced LVEDP and evoked significant (p < 0.05) decreases in LVSP (124 ± 5 to 117 ± 7 mm Hg), mean aortic pressure (85 ± 3 to 78 ± 5 mm Hg), and LV end-diastolic dimension (LVEDD) (53.0 ± 5.5 to 52.0 ± 5.7 mm), while augmenting LV dP/dt,,,, (3288 ± 266 to 3647 ± 130 mm Hg/sec). Beta blockade with IV propranolol (2.0 mg/kg) prevented the rise in LV dP/dt,,,, after high-dose NP administration but did not alter the reductions in mean aortic pressure, LVEDP, and LVEDD. This study indicates that NP, but not digitalis, has a favorable effect on LV hemodynamics in the volume-overloaded heart with normal LV systolic contraction and high-output CHF resulting from increased blood volume and reduced LV diastolic compliance. At least part of the apparent improvement in LV performance observed with high-dose NP is sympathetically mediated since it can be attenuated by beta blockade. (Am Heart J 103:489, 1982.)

Robert A. O'Rourke, M.D., Frederick R. Badke, M.D., and David Forst, M.D. San Antonio, Texas

The digitalis glycosides have been used to treat patients with congestive heart failure (CHF) for almost 200 years.1 However, there is still considerable controversy concerning the short- and long-term salutary effects of digitalis on left ventricular (LV) performance in the normal and the failing heart. While most experimental animal and patient studies have demonstrated an enhancement of LV performance by digitalis,2-17 other studies have demonstrated minor or variable improvement.18-22 The effects of the cardiac glycosides on LV performance may vary depending on the pretreatment inotropic state, the peripheral vascular resistance, the route of administration, the level of circulating...