Hemodynamic Effects of Prostaglandin E2

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Prostaglandin (PG) E_2 has been used in obstetrics for several years as a mid-trimester abortifacient. The known side effects of PGE_2 include an increase in heart rate, pyrexia in 40% of patients, and tachypnea, which are well known to obstetricians. These cases rarely come to the attention of an anesthesiologist. Although the central and peripheral effects of PGE_2 have been studied in animals, the potentially significant hemodynamic changes detectable by monitoring with a pulmonary-artery catheter are minimally explored in humans.[1,2] An increased peak cardiac output (64.5%) has been demonstrated in patients undergoing second-trimester abortion using an ultrasonic Doppler computer.[3] We report our observations in a patient with the diagnosis of preeclampsia monitored with a pulmonary-artery catheter during treatment with PGE_2.

CASE REPORT

A 30-yr-old G_2P_0 woman presented with the diagnosis of alpha thalassemia minor and an intrauterine pregnancy of an estimated 25 weeks gestation having physical and sonographic findings consistent with hydrops fetalis. At admission, the patient had generalized edema, 4+ deep tendon reflexes, 3+ proteinuria, and elevated systemic blood pressure with diastolic pressure of 85 mmHg. She was admitted for observation with the diagnosis of probable preeclampsia.

Her initial course was unremarkable, but the following morning at 6:30, rales were noted over both lung fields. A chest radiograph revealed diffuse interstitial edema indicating a diagnosis of severe preeclampsia. Her vital signs were not significantly changed from those at admission, excepting increased diastolic pressure of 90 mmHg. Arterial blood gas (ABG) and measurements while she was breathing room air revealed a pH 7.41, Pa_{CO_2} 25 mmHg, Pa_{O_2} 90 mmHg, and base deficit −6.0. An anesthesiologist was asked to evaluate the patient preoperatively in case surgical delivery was required and to insert a pulmonary-artery catheter to monitor hemodynamics. Her initial hemodynamic values were a central venous pressure (CVP) of 8 mmHg, pulmonary-artery pressure (PAP) of 37/21, and pulmonary-artery wedge pressure (PAWP) of 20 mmHg. Other laboratory values were remarkable for a white blood cell count (WBC) of 7.2×10^3, hematocrit of 29%, hypochromic, microcytic red blood cell indices (consistent with alpha thalassemia), and a platelet count of 90×10^3.

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Prothrombin and partial thromboplastin time were normal. Urinalysis revealed 3+ proteinuria and further laboratory data included a blood urea nitrogen of 20 mg%, and serum creatinine of 1.4 mg%.

Because of the maternal risks associated with eclampsia and the probable poor prognosis for the fetus, immediate vaginal delivery was recommended and the patient reluctantly agreed. The obstetrical plan at that time, 8:00 A.M., included: 1) inducing a vaginal delivery using PGE_2 vaginal suppositories at 3-h intervals to avoid the morbidity of surgical delivery; 2) phenytoin (300 mg) for seizure prophylaxis; 3) furosemide administration to achieve a PAWP < 15 mmHg; 4) restriction of fluids; and 5) supplemental O_2 administration at 6 l flow by mask. The patient was monitored by pulse oximetry (SpO_2), ECG, and PA pressures.

At approximately 10:00 A.M., anesthesia personnel were again asked to assist in patient management, including further invasive monitoring. With patient consent, we inserted an arterial catheter and recommended a urinary catheter. Her apparent response to one-quarter of a PGE_2 vaginal suppository (approximately 5 mg) she received 2 h earlier was agitation and restlessness with a heart rate (HR) of 115 beats/min in sinus rhythm. Her systemic arterial pressure (Bp) was 100/50 mmHg, respiratory rate (RR) 32/min, and urine output (U/O) averaging ≤ 0.5 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}.

At 11:00 A.M., the patient was given a half of a PGE_2 vaginal suppository (10 mg). Thirty to sixty minutes later, her agitation increased, with HR at 155 beats/min, BP 110/75 mmHg, and RR 48/min. Her temperature was 39° C, U/O unchanged, PAP 38/20 mmHg, PAWP 18 mmHg, and CVP 10 mmHg. Cardiac output (CO) was 15 l/min (by thermodilution technique), with systemic vascular resistance (SVR) of 384 dyn$\cdot$s^{-1}$\cdot$cm^5, and ABG values of pH 7.33, Pa_{CO_2} 23 mmHg, and Pa_{O_2} 170 mmHg. Mixed venous blood O_2 saturation (SvO_2) was 73%, and WBC was 16×10^3 with no left shift, 96% neutrophils. We informed the attending obstetricians that we considered some of these values consistent with, but not diagnostic of, early sepsis. Having no experience with pulmonary-artery catheter monitoring in this patient group, their clinical impression was that elevated temperature and heart and respiratory rates were probably attributable to PGE_2, but that the extent of change was excessive. The obstetrical staff decided to continue to effect a vaginal delivery, monitor the respiratory and cardiovascular status of the patient, and treat her fever with a cooling blanket, acetaminophen, and coverage with broad spectrum antibiotics. ABGs were measured every 30–60 min, appropriate blood chemistries drawn to characterize metabolic acidosis, and body fluids collected for bacterial identification and sensitivities.

Over the next 6 h, the patient remained agitated with occasional bouts of emesis and diarrhea. HR persisted at 150–160 beats/min, BP declined to 90–100 mmHg systolic, and RR increased, averaging 50 breaths/min. Temperature fluctuated, averaging 40° C, and U/O increased to 2 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}, while PAP, PAWP, and CVP decreased to 21/10 mmHg, 6–9 mmHg, and 5–7 mmHg, respectively. CO declined to 12, then 9, l/min and SVR increased from 384 to 500 to 660 dyn $\cdot$ s^{-1} $\cdot$ cm^5. At 1400 h, she had received the last 10-mg dose of PGE_2 (total 25 mg). At 1700 h, ABG measurements indicated a progressive metabolic acidosis ($pH \leq 7.30$ and base deficit to −10.4) with a consistent respiratory alkalosis (Pa_{CO_2} 23 mmHg). SpO_2 stable at 99% (F_{IO_2}: 6 l flow by mask) and SVO_2 72%.
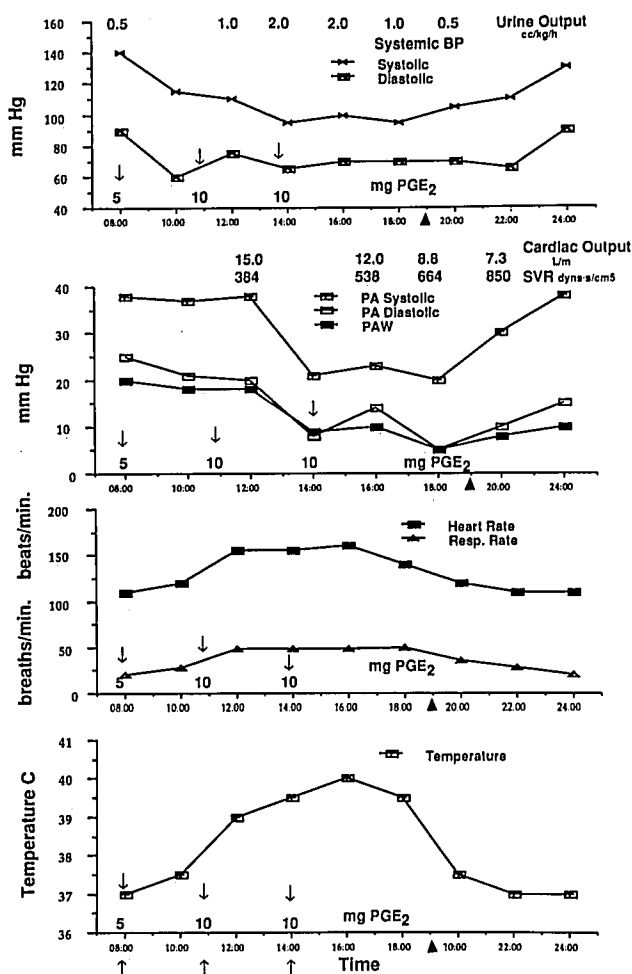
FIG. 1. Hemodynamic, respiratory, and temperature observations in a patient with preeclampsia before, during, and after administration of intravaginal PGE_2 suppositories. Delivery of the infant (▲) took place at 1930 h. SVR = systemic vascular resistance; PA = pulmonary artery; PAW = pulmonary artery wedge.

Review of the acid/base data revealed an initial non-ion-gap acidosis progressing to lactic acidosis temporally proportional to the rise in SVR and decline in CO and PAWP. We considered the most likely explanation to be excessive diuresis, probably in response to fuorsemide, and due to the high fluid requirements of a hypermetabolic state. Thus, we increased crystalloid administration to maintain adequate perfusion pressures while avoiding a reduction in the A-a O_2 gradient.

Cervical dilation had progressed to 3 cm and an oxytocin infusion was initiated to augment contractions; membranes were manually ruptured (amniotic fluid was meconium stained) and PGE_2 suppositories were discontinued. Active labor followed oxytocin infusion and persisted for approximately 1½ h, ending in vaginal delivery of a live infant whose morphological appearance was consistent with hydrops fetalis. Resuscitative efforts of the newborn were unsuccessful.

One hour before delivery, the patient's temperature and heart and respiratory rates had begun a decline to baseline values (fig. 1). The metabolic acidosis spontaneously resolved over the next 18 h after discontinuing PGE_2 administration. The following day, all antibiotics

were discontinued and, on follow-up, cultures were found to be negative. Her blood pressure remained elevated for 48 h after delivery, but 3 days later she was discharged, having had no further sequelae.

DISCUSSION

Parturients presenting with moderate to severe preeclampsia and a mid-trimester pregnancy with hydrops fetalis may have significant hemodynamic changes after PGE_2 administration. Figure 1 provides the hemodynamic data and other physiologic observations for this patient.

The temporal relationship of changes in cardiovascular and metabolic status to PGE_2 administration is evident in figure 1. Two earlier case reports deliniate similar pyrexic and hemodynamic changes after intravaginal PGE_2 to facilitate evacuation of uterine contents secondary to intrauterine fetal demise and missed abortion.[1] The authors similarly considered the etiology as endotoxemia. As with our case, all symptoms resolved with cessation of PGE_2. These authors noted a moderate hypotension and tachycardia, but only speculated on the other possible hemodynamic changes. Recently, Willis et al. noted the increase in cardiac output after PGE_2 administration.[3] Cardiac output was determined by noninvasive ultrasonic Doppler in ten women being treated with PGE_2 vaginal suppositories for mid-trimester abortions. A mean increase in peak cardiac output of 64.5% was demonstrated, but their data were limited by the lack of central vascular pressures. They also excluded patients with hypertensive disease. Secher et al. administered PGF_2 alpha and PGE_2 intravenously to women undergoing suction abortions with general anesthesia.[2] Swan-Ganz catheters and femoral artery catheters were inserted to monitor the patients. The subjects were in the first trimester of pregnancy, which excluded the circulatory changes seen in later pregnancy. Further, the patients were observed for only 30 min. However, during infusion of PGE_2, a 31% decrease in systemic blood pressure and a 33% decrease in systemic vascular resistance was noted, as well as a 36% increase in cardiac output. No note of temperature change was made and, because the patients received a general anesthetic and were given pancuronium bromide, the marked tachypnea seen in our patient could not be observed.

In the United States, PGE_2 may be the agent of choice for mid-trimester evacuation of the products of conception, especially when oligohydramniosis is present. PGE_2 has a success rate of 90% or higher over approximately 12 h, depending on the parity.[4,5] Although intravenous, intramuscular, and oral routes of administration have been tried, intravaginal suppositories allow easy, inexpensive administration, more localization to target organ, and reduced systemic exposure when compared with other routes. PGE_2 suppositories are contraindicated with

a viable fetus secondary to the risk of prolonged and uncontrollable uterine hyperstimulation. Nevertheless, low concentrations of PGE_2 in different slow-release vehicles are being investigated for topical application to dilate the cervix and increase the success of oxytocin induction at or near term pregnancy.[6-8] Oxytocin as the primary agent has a poor success rate of induction with an unripened cervix or early in pregnancy.[9,10] Some obstetricians at our institution titrate the dose of PGE_2 to the side effects, while others administer a full 20-mg suppository every 3 h and decrease the dose if the patient cannot tolerate the side effects. The most common side effects are gastrointestinal disturbances manifested by nausea, vomiting, and diarrhea. Most patients have some degree of pyrexia and heart rate elevation accompanied by a slight decrease in systemic blood pressures.[10] As a result, it is common to pretreat with antipyretics, antiemetics, and antidiarrhea medications.

When amniotic fluid is present, PGF_2 alpha had been the abortifacient of choice as an intra-amniotic injection, and the methyl analogue is now used as an intramuscular injection for the same purpose; these are drugs with which more clinicians have experience. PGE_2 has more effect on cervical dilation, which is distinct from uterine smooth muscle stimulation. PGF_2 alpha[12] acts more by direct uterine smooth muscle stimulation with less cervical dilatation, which explains why PGF_2 alpha may be used more effectively for an intramyometrial injection to control postpartum hemorrhage.[11,12] Different prostaglandin groups, such as the PGF series *versus* the PGE series, may have opposite effects on one organ while having similar effects on another organ. For example, PGF_2 alpha has little effect on heart rate and causes bronchial and vascular smooth muscle constriction, while PGE_2 has the opposite effect. Secher *et al.* demonstrated that pulmonary vascular resistance doubled with the administration of PGF_2 alpha, while there was no change with PGE_2.[2] On the other hand, both PGE_2 and PGF_2 alpha cause increased intestinal motility.[13]

The action of PGE_2 is mediated though activation of adenylate cyclase.[13] The duration of effect is 2–6 h after administration of a vaginal suppository. Cervical dilation or "ripening" is the result of enzymatic breakdown of collagen. In humans, pulmonary and systemic vasodilation has been shown to be a direct effect causing a reflex compensatory increase in cardiac output to maintain mean arterial pressure.[14,15] Animal studies have failed to show any direct inotropic effect on cardiac muscle.[16,17] PGE_2 also causes a diuresis, as seen in our patient, by virtue of increased renal blood flow secondary to renal artery dilation.[13] Direct effects upon the hypothalamus may be a separate mechanism for the increase in heart rate and

temperature.[18,19] With the observed effects of PGE_2 described in this (non-septic) case, it is not surprising that prostaglandins are being actively investigated as mediators of septic shock.[20] Enzymatic inactivation of PGE_2 into fatty acids by the lungs under normal physiologic conditions helps clear the plasma and decrease systemic effects. In addition, enzymes that catalyze the degradation of PGE_2 are found in kidneys, spleen, adipose tissue, intestine, liver, and testicles, which act to preserve the local function of prostaglandins to these organs.[14] It has been speculated that the extreme degree of side effects, as seen in our patient, may result from overwhelming the rate-limiting enzyme that inactivates prostaglandin, 15-hydroxyprostaglandin dehydrogenase, in a dose-dependent fashion or from ineffective inactivation of prostaglandins secondary to pulmonary pathology or genetic predisposition.[1]

In conclusion, we report a case demonstrating the potential of profound and often confusing side effects of PGE_2 in obstetric patients. Recent theories of the etiology of preeclampsia invoke a relative deficit of PGI_2 (prostacyclin) or PGE_2, both of which have similar effects on the cardiovascular system. In our patient, the usual signs associated with preeclampsia, including elevated systemic and pulmonary vascular resistances and decreased urine output, were reversed by PGE_2. Over the last 15 yr, prostaglandins and their inhibitors have become an increasingly important part of pharmacologic intervention in various disease states. We expect that their impact on anesthetic management will increase as the use of these agents expands to more varied medical situations.

REFERENCES

1. Phelan JP, Meguiar RV, Matey D, Newman C: Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E2. Am J Obstet Gynecol 132:28–32, 1978
2. Secher NJ, Thayssen P, Arnsbo P, Olsen J: Effect of Prostaglandin E2 and F2 alpha on the systemic and pulmonary circulation in pregnant anesthetized women. Acta Obstet Gynecol Scand 61:213–218, 1982
3. Willis DC, Caton D, Levelle JP, Banner T: Cardiac output response to prostaglandin E2-induced abortion in the second trimester. Am J Obstet Gynecol 156:170–173, 1987
4. Lauersen NH, Wilson KH: Induction of labor in patients with missed abortion and fetal death in utero with prostaglandin E2 suppositories. Am J Obstet Gynecol 127:609–611, 1977
5. Laurersen NH, Secher NJ, Wilson KH: Mid-trimester abortion induced by intravaginal administration of prostaglandin E2 suppositories. Am J Obstet Gynecol 122:947–954, 1975
6. El-Damarawy H, El-Sahwi S, Toppozada M: Management of missed abortion and fetal death in utero. Prostaglandins 14:583–590, 1977
7. Montan S, Ekman G, Sjoberg N-O, Ulmsten U: Cervical priming and/or induction by intracervical application of PGE2-gel in term patients with preeclampsia and unfavorable cervical states. Gynecol Obstet Invest 20:57–61, 1985

8. Ferguson JE, Ueland FR, Stevenson DK, Ueland K: Oxytocin-induced labor characteristics and uterine activity after preinduction cervical priming with prostaglandin E_2 intracervical gel. Obstet Gynecol 72:739–745, 1988

9. Nager C, Key T, Moore T: Cervical ripening and labor outcome with preinduction intracervical prostaglandin E2 (Prepidil) gel. J Perinatol 7:189–194, 1987

10. Rall TW, Schleifer LS: Oxytocin, prostaglandins, ergot alkaloids and other agents. The Pharmacologic and Basis of Therapeutics, 6th edition. Edited by Gilman AG, Goodman LS, Gilman A. New York, Macmillan, 1980, pp 9035–9950

11. Stys SJ, Dresser BL, Otte TE, Clark KE: Effect of prostaglandin E2 on cervical compliance in pregnant ewes. Am J Obstet Gynecol 140:415–419, 1981

12. Rayburn WF, Zuspan FP: Drug Therapy in Obstetrics and Gynecology. East Norwalk, Appleton-Century-Crofts, 1986, pp 197–204

13. Moncada S, Flower RJ, Vane JR: Prostaglandins, prostacyclin, thromboxane A_2 leukotrienes, The Pharmacological Basis of Therapeutics, 7th edition. Edited by Gilman AG, Goodman LS, Rall TW, Murad F. New York, Macmillan, 1985, pp 660–673

14. Karim SMM, Somers K, Hillier K: Cardiovascular and other effects of prostaglandins E2 aF2 alpha in man. Cardiovasc Res 5:255–259, 1971

15. Eklund B, Carlson LA: Central and peripheral circulatory effects and metabolic effects of different prostaglandins given I.V. to man. Prostaglandins 20:333–347, 1980

16. Chiba S, Malik KU: Mechanism of the chronotropic effects of prostacyclin in the dog: Comparison with the actions of prostaglandin E2. J Pharmacol Exp Ther 213:261–266, 1980

17. Staszewska-Barczak J, Dusting GJ, May DE, Nolan PN: Effects of prostacyclin on cardiovascular reflexes from the ventricular epicardium of the dog: Comparison with the effects of prostaglandin E2. Prostaglandins 21:905–915, 1981

18. Hoffman WE, Albrecht RF, Miletich DJ: Effect of sympathetic blockade on central prostaglandin E2-induced hyperthermia. Brain Res 367:73–76, 1986

19. Siren A-L: Central cardiovascular and thermal effects of prostaglandin E2 in rats. Acta Physiol Scand 116:229–234, 1982

20. Parratt JR, Sharma N, Zeitlin IJ: Prostaglandins and thromboxane in the delayed phase of shock induced by Serratia marcescens endotoxin. Br J Pharmacol 82:281–288, 1984