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Prostaglandin $F_{2\alpha}$ Attenuation of Aortic Declamping Hyperemia and Hypotension[1]

LINDA M. GRAHAM, M.D.,[2] JAMES C. STANLEY, M.D., BRUCE L. GEWERTZ, M.D., GERALD B. ZELENOCK, M.D., AND WILLIAM J. FRY, M.D.

Section of General Surgery, Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan 48104

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Transient infrarenal aortic occlusion is a necessary accompaniment of most vascular reconstructions of the distal aorta and its terminal branches. In certain instances systemic hypotension follows restoration of extremity blood flow. Severe hypotension may occasionally compromise cardiac, cerebral and renal perfusion. Associated with this aortic declamping phenomenon is a severalfold increase in blood flow to the ischemic extremities. Although precise mechanisms are poorly defined, reactive hyperemia is in part responsible for the declamp hypotension.

Reliable, safe means to ameliorate declamp hypotension do not exist. Rigorous volume replacement, intraoperative administration of buffers, and vasopressors have been utilized to lessen this hazard of aortic surgery. Unfortunately, injudicious transfusions, fluid overloading, and systemic vasopressors may prove harmful to elderly patients with marginal cardiac and renal reserves. The present investigation was undertaken to determine what role the vasopressor prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) might have in the prevention of aortic declamp hyperemia and hypotension.

MATERIALS AND METHODS

Effects of $PGF_{2\alpha}$ were documented in a canine model during consecutive clamping and declamping trials. Individual animals acted as their own control. Trials I and III (base line studies) involved infusions of phosphate buffer into the terminal aorta at the time of declamping. Trials II and IV (experimental studies) differed in that $PGF_{2\alpha}$ was added to the buffer.

Ten male mongrel dogs, weighing 17–35 kg, were studied. All animals were anesthetized with sodium pentobarbital 30 mg/kg with supplemental doses administered at 30 min intervals as needed. Dogs were intubated, mechanically ventilated, and hydrated with lactated Ringers' (100 ml/hr) throughout the experiment. Animals were systemically anticoagulated with sodium heparin (100 units/kg iv). The aorta and iliac vessels were exposed through a midline abdominal incision. An adjustable clamp was placed about the infrarenal aorta for later use in occluding this vessel. A polyethylene catheter for infusion purposes was advanced into the terminal aorta by way of the spermatic artery.

Left carotid artery and external jugular vein polyethylene catheters were positioned within the aorta and superior vena cava respectively. Electromagnetic square wave flow probes were placed on the right carotid and iliac arteries. Flow probes were zeroed electrically and mechanically with each study. A small catheter was inserted into the right femoral vein for blood sampling. Systemic arterial pressure, central venous pressure, iliac and carotid artery blood flows were recorded.

Following documentation of base line

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[2]Correspondence to Dr. Graham, University of Michigan Medical Center, 1405 E. Ann Street, Ann Arbor, Michigan 48109.

pressures and flows, the infrarenal aorta was clamped for 30 min (Trial I). At the conclusion of the clamp period, 12.5 ml of phosphate buffer (0.2 M, pH 6.5) were infused into the terminal aorta over a 30 sec period prior to declamping. An additional 12.5 ml were infused during a 10 sec period immediately following declamping. Pressure and blood flow were continuously monitored with restoration of flow to the lower extremities. A recovery period of 30 min was allowed, and the aorta was reclamped for a second 30 min (Trial II). Declamping technique terminating this second period of occlusion was similar in all respects to that of Trial I except for the addition of 20 μg/kg of prostaglandin $F_{2\alpha}$ tromethamine salt to the 25 ml phosphate buffer solution. Identical recovery, clamp and declamp methodology was utilized for a second base line buffer infusion (Trial III) and with a second experimental $PGF_{2\alpha}$ infusion (Trial IV). Hemodynamic measurements obtained during these studies, reflecting different declamp responses, were expressed as the mean ± 1 SD, and analyzed by paired *t* test.

Femoral venous, central venous, and carotid artery blood pH, pO_2 and pCO_2 were documented prior to clamping, immediately before declamping and 30 sec after declamping in five dogs. In five other animals prostaglandin B_1 (PGB_1) and $PGF_{2\alpha}$ activities were assayed in femoral vein and carotid artery blood samples. Specimens were collected immediately preceding clamping as well as 5 sec and 5 min following declamping. PGB_1 levels were determined after conversion of prostaglandins A and E (PGA, PGE) to the former substance. Radioimmunoassay technique using specific antibodies for PGB_1 and $PGF_{2\alpha}$ were used to quantitate prostaglandin activity (Clinical Assays Inc., Cambridge, Mass.).

RESULTS

Blood pressure and flow alterations observed in Trial I (first base line study) and Trial II (first experimental study) were markedly different (Table I). Decreases in systemic arterial blood pressure with declamping and $PGF_{2\alpha}$ infusions in Trial II averaged 11 ± 7 mm Hg. This change in pressure was significantly less ($P < 0.01$) than the 27 ± 8 mm Hg decrease occurring in earlier control (Trial I) studies.

Reactive hyperemia, reflected by maximum iliac artery blood flow following declamping, was diminished after administration of $PGF_{2\alpha}$ (Trial II) in comparison to controls (Trial I). Peak flows in these instances were 208 ± 104 and 334 ± 143 ml/min, respectively. Differences in these hyperemic responses proved significant ($P < 0.01$). Marked hyperemic responses occurred immediately with declamping in control (Trial I) dogs (Fig. 1). Blunting of the hyperemic response was evident (Fig. 2) following initial $PGF_{2\alpha}$ infusion (Trial II). In certain cases hyperemia was attenuated by $PGF_{2\alpha}$, yet *total* blood flow to the ischemic extremities over 2–3 min approximated control flow volumes.

Decreases in peripheral blood flow (carotid artery) observed after initial aortic declamp-

TABLE I[a]

Trial	Systemic (aortic) pressure (mm Hg)			Peripheral (carotid) arterial blood flow (ml/min)			Ischemic extremity arterial (iliac) blood flow (ml/min)		
	Pre-declamp	Post-declamp	Δ	Pre-declamp	Post-declamp	Δ	Pre-clamp	Post-declamp	Δ
I. Buffer	129 ± 22	103 ± 20	−26.8	209 ± 47	160 ± 44	−49.5	84 ± 34	334 ± 143	+250.0
II. $PGF_{2\alpha}$	125 ± 20	114 ± 20	−10.6*	168 ± 44	151 ± 38	−17.5*	90 ± 26	208 ± 104	+172.0*
III. Buffer	123 ± 22	115 ± 21	−30.0	156 ± 52	117 ± 26	−37.8	90 ± 33	360 ± 159	+270.0
IV. $PGF_{2\alpha}$	127 ± 20	102 ± 21	−24.8	159 ± 48	129 ± 43	−29.4	102 ± 44	338 ± 226	+235.6

[a]Data expressed as mean ± 1 SD.

*Significant differences ($P < 0.01$) comparing changes (Δ) in Trial II to Trials I and III; paired *t* test. No statistical differences demonstrable among changes (Δ) observed in Trials I, III and IV. Paired *t* test.

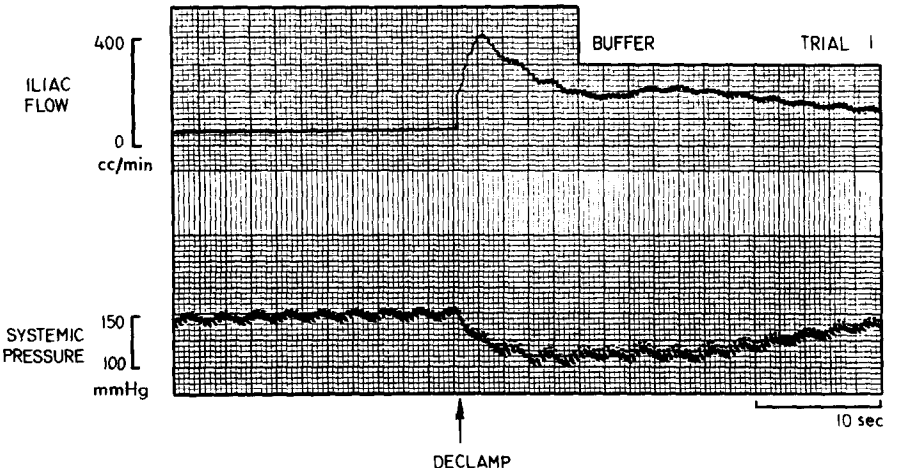

FIG. 1. Buffer infusion at the time of aortic declamping followed by marked increase in iliac artery blood flow with associated decrease in systemic blood pressure.

ings (Trial I) were diminished by infusions of $PGF_{2\alpha}$ (Trial II). Carotid flow in controls decreased 50 ± 18 ml/min at declamping (Trial I) in comparison to an 18 ± 22 ml/min decrease after $PGF_{2\alpha}$ administration (Trial II). These differences were significant ($P < 0.01$).

An unanticipated finding was that repeated administration of $PGF_{2\alpha}$ (Trial IV) did not effect results similar to those observed after initial $PGF_{2\alpha}$ infusion (Trial II). Pressures and flows observed in Trial III (second base line study) and Trial IV (second experimental study) showed little variance (Table 1). Mean decrease in systemic arterial pressure following declamping in Trial I (27 ± 8 mm Hg) did not vary statistically from that noted in Trial III (30 ± 13 mm Hg) or Trial IV (25 ± 11 mm Hg). Preclamp blood pressures and pressure changes during aortic clamping were not related to the magnitude of postdeclamp hypotension or effects of $PGF_{2\alpha}$ infusions. Similarly, alterations in blood gases or pH did not seemingly affect the degree of declamp hypotension or $PGF_{2\alpha}$ responses.

Assay of systemic arterial and ischemic extremity venous PGB_1, reflecting PGA,

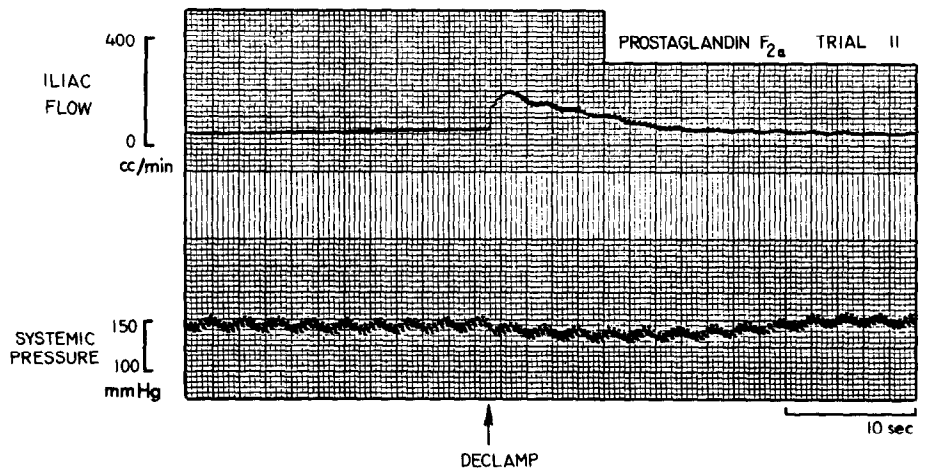

FIG. 2. $PGF_{2\alpha}$ infusion at the time of aortic declamping causing moderate increase in iliac artery blood flow and minimal decrease in systemic blood pressure.

TABLE 2[a]
Prostaglandin B_1 (PGB and Converted PGA–PGE)

Trial		Preclamp	Postdeclamp 5 sec	Postdeclamp 5 min
I. Buffer	Systemic arterial	7.1 (2.4–10.1)	7.8 (5.8–10.2)	6.6 (5.7–7.8)
	Ischemic extremity venous	10.1 (8.9–12.7)	9.5 (7.5–11.6)	6.7 (5.5–7.9)
II. $PGF_{2\alpha}$	Systemic arterial	6.9 (4.3– 8.9)	6.6 (4.1– 9.2)	4.8 (4.0–6.0)
	Ischemic extremity venous	8.3 (4.9–12.7)	5.5 (3.3– 8.1)	7.8 (4.6–9.8)
III. Buffer	Systemic arterial	6.0 (2.6– 7.8)	6.1 (3.8– 8.6)	4.1 (3.1–5.7)
	Ischemic extremity venous	6.6 (3.1–11.0)	4.8 (3.4– 7.8)	4.3 (4.2–4.5)
IV. $PGF_{2\alpha}$	Systemic arterial	4.6 (2.1– 6.6)	4.9 (2.3– 7.9)	5.1 (1.3–7.4)
	Ischemic extremity venous	5.2 (1.5–10.8)	5.7 (2.7–10.2)	4.5 (1.4–6.3)

[a]Data (ng/ml) expressed as mean and (range).

PGB and PGE activity, did not demonstrate significant increases of these substances as the experiment progressed from Trials I to IV (Table 2). Elevated $PGF_{2\alpha}$ was documented in ischemic extremity effluent blood 5 sec following declamping in experimental Trials II and IV, confirming high levels of this agent being delivered with aortic infusions (Table 3). Measurements of $PGF_{2\alpha}$ revealed increased venous levels from the ischemic extremity after the first $PGF_{2\alpha}$ infusion of Trial II which persisted into Trial III.

DISCUSSION

Hemodynamic changes following aortic declamping are well known, yet exact mechanisms underlying these events are poorly understood. Declamp reactive hyperemia is thought to be primarily a reflex phenomenon rather than a sole consequence of local metabolic alterations [7]. The theory that increases in the vascular compartment of ischemic extremities cause pooling of blood away from the central circulation, is compatible with observations of increased canine hindlimb volumes following declamping [18, 19]. The basis for this change in the vascular compartment is unknown.

Prostaglandins are known for their vasoactive properties. The E and A series are primarily vasodepressors. Cardiovascular actions of the F series are complicated by species variation. $PGF_{2\alpha}$ exerts a pressor action in dogs, rats, and man [4, 11, 12, 14–17]. Most investigators agree that $PGF_{2\alpha}$ causes constriction of canine capacitance vessels. DuCharme and his colleagues [4] observed that infusions of $PGF_{2\alpha}$ into perfused canine limbs increase peripheral resistance with constriction of smooth muscle of veins rather than arterioles. This increases venous return, right atrial pressure and subsequently cardiac output. Others reported $PGF_{2\alpha}$ to have a direct cardiac effect, increasing myocardial contractility and heart rate [6, 16]. Although $PGF_{2\alpha}$ apparently has a primary

TABLE 3[a]
Prostaglandin $F_{2\alpha}$

Trial		Preclamp	Postdeclamp 5 sec	Postdeclamp 5 min
I. Buffer	Systemic arterial	1.9 (1.0– 3.0)	2.4 (2.0– 3.0)	2.3 (1.5– 3.3)
	Ischemic extremity venous	2.4 (1.9 2.9)	2.7 (1.9– 3.3)	2.1 (1.4– 3.3)
II. $PGF_{2\alpha}$	Systemic arterial	2.0 (1.4– 2.8)	24.5 (10.0– 40.0)	4.1 (2.6– 7.2)
	Ischemic extremity venous	2.2 (1.4– 3.0)	485.0 (69.0–750.0)	48.6 (12.0–97.0)
III. Buffer	Systemic arterial	2.2 (0.9– 3.4)	2.6 (1.1– 4.7)	1.8 (1.0– 3.4)
	Ischemic extremity venous	14.5 (7.1–25.0)	95.6 (3.1–413.0)	6.9 (2.5–11.0)
IV. $PGF_{2\alpha}$	Systemic arterial	4.6 (1.1–13.0)	28.7 (2.4– 50.0)	6.8 (2.1–14.0)
	Ischemic extremity venous	13.8 (2.6–44.0)	338.2 (9.7–468.0)	28.6 (5.9–54.0)

[a]Data (ng/ml) expressed as mean and (range).

effect on venous segments, it also has vasoconstrictive effects on other portions of the peripheral vascular bed. Increased vascular resistance, decreased blood flow and constriction of skeletal muscle arteries in response to $PGF_{2\alpha}$ have been described [6, 8, 13].

Mechanisms of $PGF_{2\alpha}$ action are poorly defined. This substance may directly stimulate vascular smooth muscle. $PGF_{2\alpha}$ also interacts with the autonomic nervous system. Infusion of $PGF_{2\alpha}$ intra-arterially in subpressor concentrations enhances vasoconstrictor responses to sympathetic nerve stimulation in the canine hindlimb. $PGF_{2\alpha}$ appears to enhance sympathetic transmission, by facilitating release of neurotransmitters at the nerve ending [1, 9, 10].

The role of $PGF_{2\alpha}$ pressor activity in humans remains unclear. Some investigators found $PGF_{2\alpha}$ given as a single intravenous injection (500 μg), increased arterial blood pressure, whereas when infused intravenously (4 μg/kg/min) and administered subcutaneously or intramuscularly (20 mg) it had no cardiovascular effect [11]. Infused into superficial hand veins of man, $PGF_{2\alpha}$ (200–500 ng/min) has a vasoconstrictor effect [2]. Subconstrictor dosages were not associated with depressor activity. In forearm arterial beds, $PGF_{2\alpha}$ infusion (2–10 μg/min) increased blood flow [3]. Constrictor responses were noted in this later study at lower infusion levels (0.4–2 μg/min).

Present experimental observations. Initial infusions of $PGF_{2\alpha}$ into the terminal aorta with aortic declamping attenuated the reactive hyperemic response and subsequent systemic arterial hypotension. $PGF_{2\alpha}$ may constrict hindlimb capacitance vessels, thus limiting expansion of the ischemic extremities' vascular compartment. $PGF_{2\alpha}$ may also enhance normal sympathetic vasoconstrictor activity accompanying declamp hypotension. Additional studies in isolated and denervated hindlimbs are needed to define exact

mechanisms of $PGF_{2\alpha}$ action in this particular experimental model.

An important finding of the present investigation was that $PGF_{2\alpha}$ lessened declamp hypotension following its initial administration (Trial II), but was not subsequently effective (Trial IV). This phenomenon remains unexplained. Failure to effect changes with repeat $PGF_{2\alpha}$ infusions, despite documentation of high circulating levels of this prostaglandin within the ischemic extremity circulation, suggests a tachyphylactic response. Increased $PGF_{2\alpha}$ levels during Trial III, when no $PGF_{2\alpha}$ was administered, implies the existence of persistently elevated tissue levels of this substance. Studies by others [5] lend credence to the possibility that tachyphylaxis accounts for the nonresponsiveness to repeated $PGF_{2\alpha}$ infusions. Accumulation of prostaglandin precursors following degradation of $PGF_{2\alpha}$, inducing production of E and A series prostaglandins was not supported by measurements of these prostaglandins in the present investigation.

Circulating $PGF_{2\alpha}$ is inactivated with passage through the lungs. Infusions of $PGF_{2\alpha}$ into the terminal aorta should thus have rather localized effects. Since $PGF_{2\alpha}$ activity most consistently involves capacitance (venous) vessels, reversal or prevention of venodilation may be its primary action in the presently reported preparation. Pressor and venoconstrictor properties of $PGF_{2\alpha}$ combined with pulmonary degradation of this substance, make it unique in regard to its cardiovascular actions. $PGF_{2\alpha}$ may be of potential use in lessening adverse effects of aortic declamping, such as with sleeve resection of the infrarenal aorta or following temporary occlusions while revascularization of the splanchnic viscera or kidneys is being performed. $PGF_{2\alpha}$ infusions would appear to be of limited value in situations requiring repeated administrations, such as with staged declamping of aortofemoral graft limbs. Further investigation is warranted to evaluate the efficacy of $PGF_{2\alpha}$ in attenuating hyperemic responses and subsequent systemic arterial hypotension as a sequela of aortic declamping in the clinical setting.

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