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Volume 1, Numbers 3/4, December 1989

Editorial: letter to our readers	145
Letters to the Editors	147
Current status of penile prostheses T.R. MALLOY AND A.J. WEIN	153
Bacterial adherence to penile prostheses J.A. ROBERTS, E.N. FUSSELL AND R.W. LEWIS	167
Infected penile prostheses: incidence and outcomes B. FALLON AND H. GHANEM	175
Effects of noradrenaline, 5-hydroxytryptamine and histamine on human penile cavernous tissue and circumflex veins H.J. KIRKEBY, A. FORMAN, S. SORENSEN AND K.-E. ANDERSSON	181
Assessment of the alpha-adrenergic receptors in isolated human and canine corpus cavernosum tissue K. KIMURA, Y. KAWANISHI, M. TAMURA AND A. IMAGAWA	189
Intracavernous injections of solutions with different osmolarity and pH in the rabbit W. STACKL, C.G. STIEF, F. BENARD, S.R. ABOSEIF, R.J.L.H. BOSCH, G. LOUPAL, T.F. LUE AND E.A. TANAGHO	197
Detumescent effect of clonidine on penile erection J.S.-N. Lin, P.-C. Yu, M.C.M. Yang and J.-S. Kuo	201
Changes in penile hemodynamics after intracavernous injection of prostaglandin E ₁ and prostaglandin I ₂ in pigtailed monkeys R.J.L.H. BOSCH, F. BENARD, S.R. ABOSEIF, C.G. STIEF, W. STACKL, T.F. LUE AND E.A. TANAGHO	211
Abstracts of the Second Biennial Asia-Pacific Meeting on Impotence	223
Recent and forthcoming scientific meetings	255
Errata: Volume 1, 95-113	256
Author index to volume 1 (1989)	257
Keyword index to volume 1 (1989)	258

Changes in penile hemodynamics after intracavernous injection of prostaglandin E₁ and prostaglandin I₂ in pigtailed monkeys

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We investigated the hemodynamic changes induced by intracavernous injection of 5, 10 and 20 µg of prostaglandin I₂ (PGI₂) in 11 monkeys.

Cavernous arterial blood flow increased for a mean duration of 20 min after intracavernous injection of 20 µg PGE₁, as detected by ultrasound and pulsed Doppler studies. The degree and duration of cavernous smooth muscle relaxation after PGE₁ injection was dose-dependent, as demonstrated in cavernous perfusion studies. Venous occlusion occurred in only four of 11 monkeys with doses up to 20 µg PGE₁.

After intracavernous injection of PGI₂ no increase in cavernous arterial blood flow could be detected by ultrasound and pulsed Doppler studies. There was a large reduction of the cavernosal compliance owing to smooth muscle contraction with PGI₂ doses of 100 and 200 µg.

PGI₂, in contrast to PGE₁, does not appear to be beneficial in the diagnosis and treatment of impotence.

Keywords: penis, hemodynamics, injection, prostaglandin, monkeys.

The attainment of a full erection depends upon three hemodynamic phenomena: increased flow in the cavernous arteries; cavernous smooth muscle relaxation, and venous outflow restriction¹. The ability of vasoactive drugs to induce erection depends upon the ability of these agents to induce relaxation of cavernous and arterial smooth muscle cells. Various drugs, including papaverine², the alpha-blocker phenoxybenzamine³, and vasoactive intestinal polypeptide⁴, have been shown to possess this ability. The intracavernous injection of papaverine or of a combination of papaverine and the alpha-blocker phentolamine has gained widespread acceptance in the treatment of impotence⁵⁻⁸. However, side-effects such as priapism^{5,9}, fibrous plaque formation¹⁰, hypotension, dizziness and facial flushing, and the destruction of normal cavernous architecture after prolonged use¹¹ have been reported.

PGE₁ does not appear to elicit severe side-effects^{11,12}, and it has been shown to be efficacious in several clinical trials¹²⁻¹⁵. In-vitro, PGE₁ is able to relax both

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cavernous smooth muscle strips and segments of the cavernous artery that have been contracted by noradrenaline¹⁶. In vivo, it increases blood flow in the cavernous artery in humans¹⁷.

In vitro, PGI₂ relaxes cavernous arterial segments and causes cavernous smooth muscle strips to contract. Hedlund and Andersson¹⁶ suggest that it might increase cavernous arterial blood flow in the initial phase of erection and therefore might have a role in the treatment of impotence. The full range of in-vivo effects of PGE₁ and PGI₂ on the penis is not yet well established. We therefore studied the hemodynamic effects of intracavernous injection of PGE₁ and PGI₂ in the monkey, whose penis closely resembles the human.

MATERIALS AND METHODS

Eleven pigtailed monkeys (*Macaca nemestrina*), all less than 10 years old and weighing 4.5–7.5 kg, were used to study the changes in penile hemodynamics after intracavernous injection of PGE₁ (Upjohn) or PGI₂ (Upjohn). For all experiments the chosen doses of PGE₁ (5, 10 or 20 µg) or PGI₂ (100 or 200 µg) were diluted in 1 ml of normal saline. Dilutions were freshly prepared for each experiment.

Four sets of experiments were performed, as follows.

- (1) Intracavernous drug injection, with recording of the intracavernous pressure before and after delivery.
- (2) Saline perfusion of the corpora cavernosa at a fixed rate before and after intracavernous drug injection¹⁸. Differences in the plateau pressure attained before and after reflect drug-induced changes in cavernous compliance.
- (3) Pulsed Doppler ultrasound studies of cavernous arterial flow.
- (4) Controlled infusion of saline into the cavernous bodies during periods of intermittent clamping of the aorta to study venous occlusion.

Owing to the limited availability of the monkeys used, it was not the intention of this investigation to represent a complete dose-response study.

EXPERIMENT 1

After anesthesia with ketamine (30 mg/kg body weight, IM), the monkeys were placed in the supine position. Under sterile conditions a 21-gauge scalp-vein needle was placed in the distal part of each cavernous body away from the vestigial penile bone. One needle was connected to a Statham transducer (model P23 BC) and used for recording the intracavernous pressure on a Grass Polygraph (Model 7). The other needle was used for intracavernous injection or saline perfusion. Penile tumescence was observed visually and noted in relation to the pressure changes. Injections with each dose of PGE₁ or PGI₂ were given twice on separate occasions (except for monkeys 9, 10 and 11 who received only one 20-µg dose of PGE₁ during an acute experiment). The penis was not massaged in order not to disturb the carefully placed intracavernous needles.

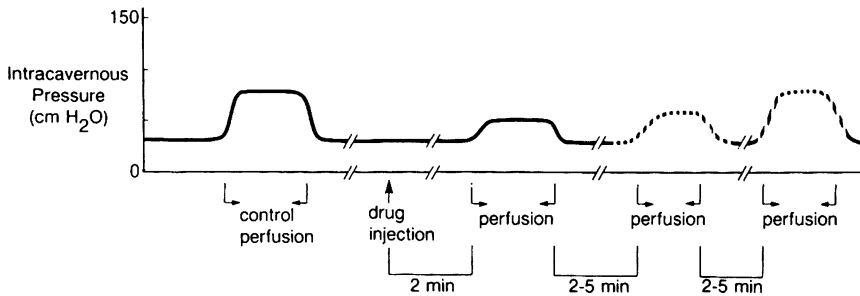


FIGURE 1. Perfusion protocol: A baseline measurement ("control perfusion") during saline perfusion at 11.5 ml/min is first obtained, and the drug is then injected intracavernously. Measurement is repeated at 2- to 5-min intervals until the plateau pressure has returned to the baseline value.

EXPERIMENT 2

Perfusion protocol (see Figure 1). Saline was perfused at the rate of 11.5 ml/min for about 1 min (Harvard perfusion pump) and the plateau pressure was recorded. In preliminary studies this perfusion rate led to only minimal penile elongation and a baseline plateau pressure of about 60 cm H₂O in most monkeys. It proved to be a convenient rate for comparison of plateau pressures before and after pharmacologic manipulations.

After the above measurement, perfusion at the same rate and for the same duration was repeated within 2 min after intracavernous injection of a drug. The resulting plateau pressure was compared with the baseline plateau. To measure the duration of the drug's action, subsequent saline perfusions of the same rate and duration were repeated at regular intervals without further drug injection. The end of the drug's action was defined as that point at which the plateau pressure returned to baseline. It is possible, however, that the repeated perfusions washed out the drug and thereby decreased the apparent duration of action. Doses of 5 μ g ($n = 4$), 10 μ g ($n = 8$) or 20 μ g ($n = 5$) of PGE₁ and 100 μ g ($n = 4$) or 200 μ g ($n = 6$) of PGI₂ were tested. Each dose was given twice. The second trial was performed after the perfusion plateau had returned to its baseline value. In Results, the mean value of these two trials is used.

EXPERIMENT 3

To examine possible changes in the arterial flow, we performed pulsed Doppler ultrasound studies of the cavernous artery¹⁹ in monkeys 1, 2, 4, 5, 6, 7 and 8 before and after intracavernous drug injection. The monkeys were anesthetized as before, and the flow velocity in the cavernous artery before and after injection of 20 μ g PGE₁ or 200 μ g PGI₂ was measured.

EXPERIMENT 4

Three monkeys, 9, 10 and 11, were used to study the possible occurrence of venous outflow restriction. With the same basic set-up as described above, the abdominal cavity was opened through a midline incision and the infrarenal aorta was exposed for intermittent clamping with a Satinsky clamp. While the aorta was clamped, the cavernous bodies were perfused at a rate of 11.5 ml/min before and after injection of 20 μ g PGE₁. Because Experiments 1 and 2 had shown that PGI₂ induced penile

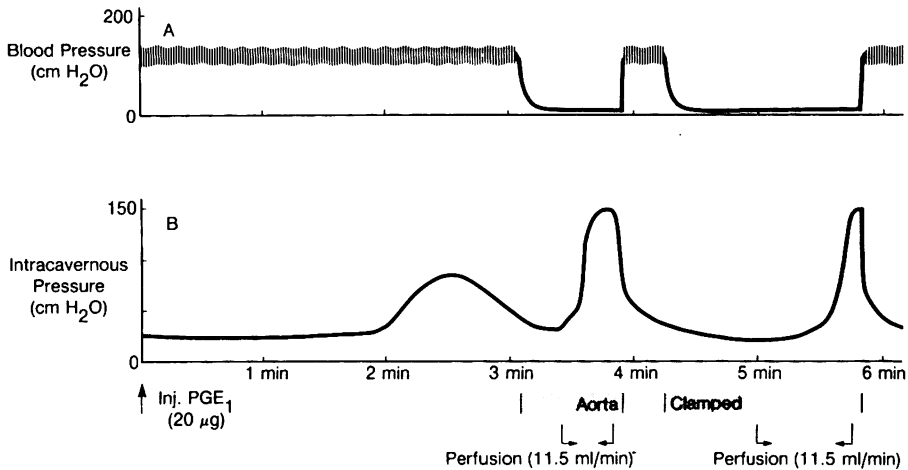


FIGURE 2. After 20 μg PGE₁ in one monkey, the intracavernous pressure rose briefly after the initial slight drop. In the venous occlusion study, cavernous perfusion of saline after clamping of the aorta led to an off-scale pressure rise after about 10 s. In subsequent perfusion, more time was needed to reach an off-scale pressure, reflecting the waning of the action of PGE₁.

shrinkage only (see Results), this experiment was performed only with PGE₁. Blood pressure was recorded through an 18-gauge needle in the right femoral artery.

RESULTS

EXPERIMENT 1

In monkeys 1 through 8, intracavernous injection of 5 μg ($n = 4$), 10 μg ($n = 8$) and 20 μg ($n = 5$) of PGE₁ was followed by a drop in the intracavernous pressure

TABLE 1. Pressure plateau during saline perfusion after PGE₁ or PGI₂*.

Monkey	PGE ₁			PGI ₂	
	5 μg	10 μg	20 μg	100 μg	200 μg
1	N.D.	50%	38%	N.D.	107%
2	28%	25%	10%	N.D.	194%
3	N.D.	54%	O.S.	N.D.	125%
4	40%	35%	O.S.	135%	N.D.
5	N.D.	O.S.	N.D.	142%	N.D.
6	N.D.	93%	87%	110%	O.S.
7	42%	37%	N.D.	114%	104%
8	O.S.	O.S.	N.D.	N.D.	115%

*Rate of saline perfusion = 11.5 ml/min. The plateau pressure attained with perfusion before drug injection = 100%. Values are means of the results of 2 trials.
N.D. = not done. O.S. = out of scale (>180 cmH₂O).

that was both brief and slight (<20 s; <15 cmH₂O). None of these monkeys exhibited a subsequent rise in intracavernous pressure above the pre-injection value, although some penile elongation was seen in all. However, monkey 9 (an acute study) exhibited an increase in the intracavernous pressure (see Figure 2) with a dose of 20 μ g.

Intracavernous injection of PGI₂ in doses of 100 μ g ($n = 4$) and 200 μ g ($n = 6$) resulted in a shrinkage or a decrease in length of the penis. This made pressure recording very difficult as the recording needle tended to become blocked despite repeated flushing with heparin. This clear response seen in all monkeys suggested a strong contraction of the cavernous smooth muscles.

EXPERIMENT 2

In monkeys 1 through 8, the baseline plateau pressure with perfusion ranged between 48 and 112 cmH₂O. However, each animal's baseline plateau pressure was defined as 100%; thus, differences were due to variations in penile size and baseline compliance.

PGE₁ RESULTS. Table 1 summarizes the percentages of the baseline plateau pressures reached during perfusion, about 2 min after administration of various doses of PGE₁. Two different types of reaction were seen.

In the first type (see Figure 3) the plateau pressure after drug administration was lower than the baseline plateau. This was seen in monkeys 1, 2, 6 and 7 (with all doses), 3 (with 10 μ g only), and 4 (with 5 and 10 μ g). In monkeys in which different dosages were used, the pressure was always lower with the higher dose (see Table 1). The lowering of the pressure plateau was always accompanied by penile elongation, owing to cavernous smooth muscle relaxation and a higher cavernous compliance.

The second type of response (see Figure 4) was an intracavernous pressure increase that was initially attenuated with respect to the baseline plateau, but which then increased rapidly to off-scale levels — the reaction seen in monkeys 3

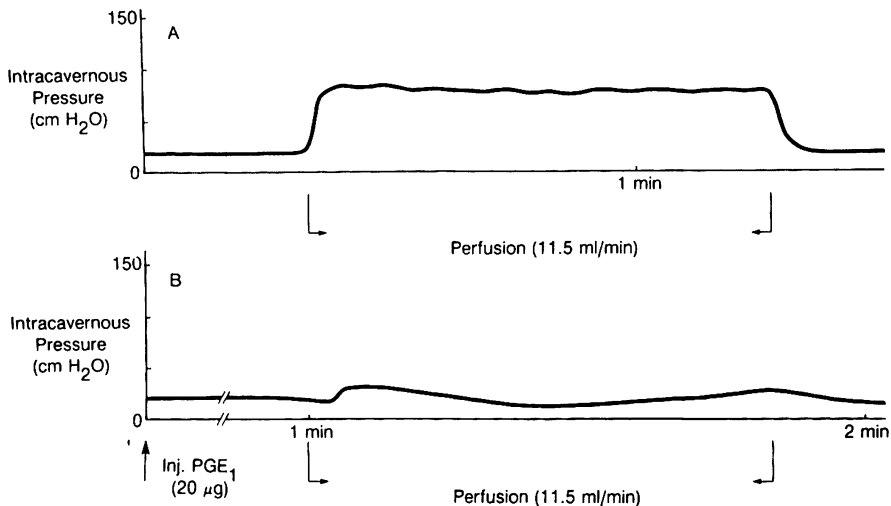


FIGURE 3. Example of first type of reaction (see text) before (A) and after (B) injection of PGE₁. The plateau pressure is significantly decreased, and penile tumescence and elongation occur.

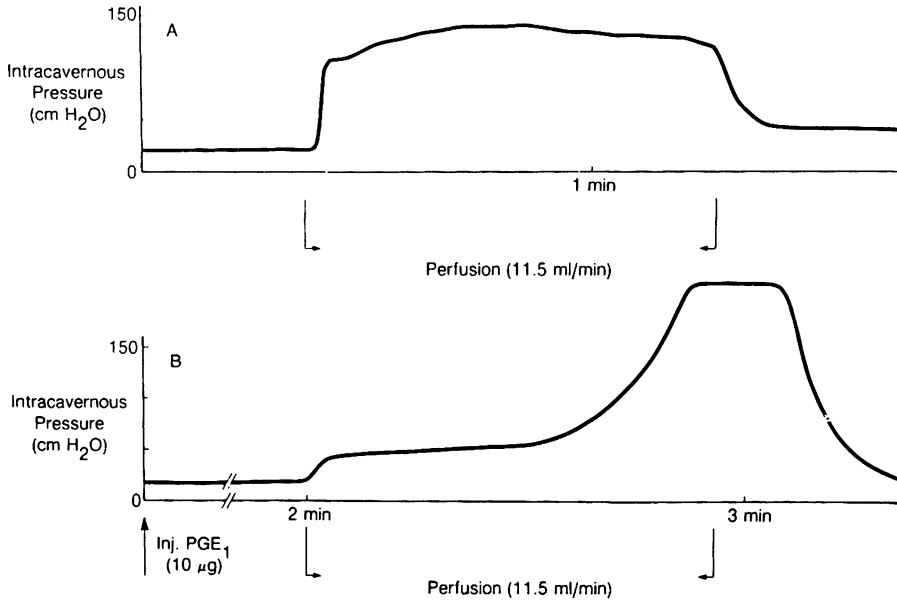


FIGURE 4. Example of the second type of reaction (see text) before (A) and after (B) PGE₁. The plateau pressure is initially less than the baseline plateau pressure (A) and then rises off the scale (B), concurrent with full penile erection.

and 4 (with 20 µg), 5 (with 10 µg), and 8 (with 5 µg and 10 µg), always accompanied by full penile rigidity. This type of reaction results from initial cavernous smooth muscle relaxation followed by complete venous outflow restriction.

The duration of the drug's action was measured by repeated perfusions at 2- to 5-min intervals until the plateau pressure returned to baseline. Plateau pressures recovered within 8-15 min (mean: 13.5 min) after the 5-µg dose and within 17-25 min (mean: 20 min) and 12-30 min (mean: 20.5 min) with 10 µg and 20 µg, respectively.

PGI₂ RESULTS. Table 1 lists the plateau pressures associated with administration of 100 µg or 200 µg PGI₂. These were always higher than the baseline value. For example, in monkey 6, 200 µg PGI₂ resulted in a plateau pressure that rose off the scale (> 180 cmH₂O). The higher pressures after PGI₂ administration were invariably accompanied by penile shrinkage.

Although repeated perfusions may have washed out PGI₂ and might have decreased the duration of its action, the plateau pressure returned to baseline within 8-10 min (mean: 9 min) after 100 µg and within 7-21 min (mean: 13 min) after 200 µg. Interestingly, in four of the eight monkeys, the arterial pulsations that were superimposed on the cavernous pressure recording were of a larger amplitude after PGI₂ than before (see Fig 5).

EXPERIMENT 3

In monkeys 1, 2, 4, 5, 6, 7 and 8, the cavernous arteries were studied with pulsed Doppler ultrasound before and after intracavernous injection of 20 µg PGE₁ and before and after injection of 200 µg PGI₂. The signal from the cavernous artery

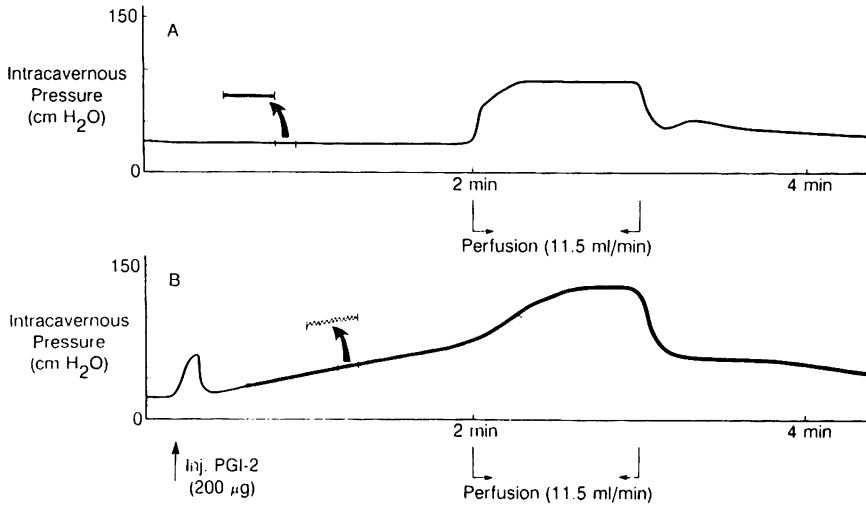


FIGURE 5. Intracavernous pressure before (A) and after (B) injection of 200 μg PGI₂. After injection but before the start of saline perfusion, the intracavernous pressure increases, accompanied by penile shrinkage. The plateau pressure during perfusion is higher than before PGI₂ injection, although the penis is shrunken at this time. Note also the increased amplitude of arterial pulsations (arrows) superimposed on the intracavernous pressure after PGI₂ injection.

was not detectable in any of the seven monkeys before injection.

PGE₁ RESULTS. The peak flow velocity in the cavernous artery could be measured after injection in six of the seven monkeys (Table 2 and Figure 6). The measurement was repeated periodically until no signal could be detected. The peak flow velocity occurred 4-28 min (mean 12.5 min) after PGE₁ injection. However, in any animal the true maximum could have been missed because the measurements were not continuous (relocating the cavernous artery determined the timing). The drug's reported duration of action on cavernous arterial flow also represents an estimate: we recorded the time at which a signal was detected for the last time (ranging between 14 and 32 min; mean 18.5 min) and the first time at which the signal could no longer be detected (ranging between 10 and 30 min; mean 23.5 min). The actual duration of action lies between these two values.

TABLE 2. Pulsed Doppler ultrasound of the cavernous arterial flow after 20 μg PGE₁.

Monkey	Peak flow velocity (cm/s)	Time of maximal response (min)*	Duration of flow increase (min)
1	14	8	13-18
2	15	9	10-14
4	47	13	29-32
5	24	4	15-20
6	29	13	14-25
7	24	28	30-32
8†	-	-	-
mean	25.5	12.5	18.5-23

*See text.

†undetectable.

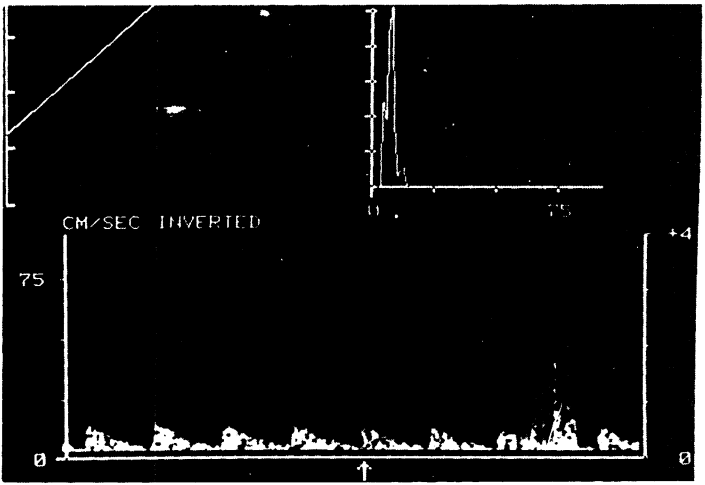
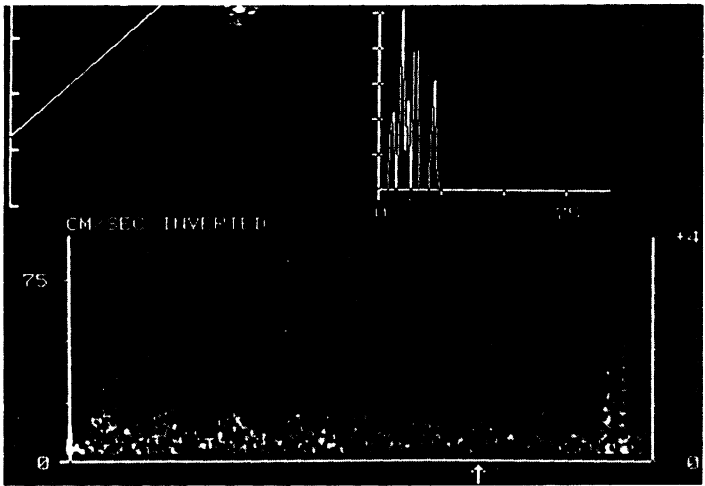
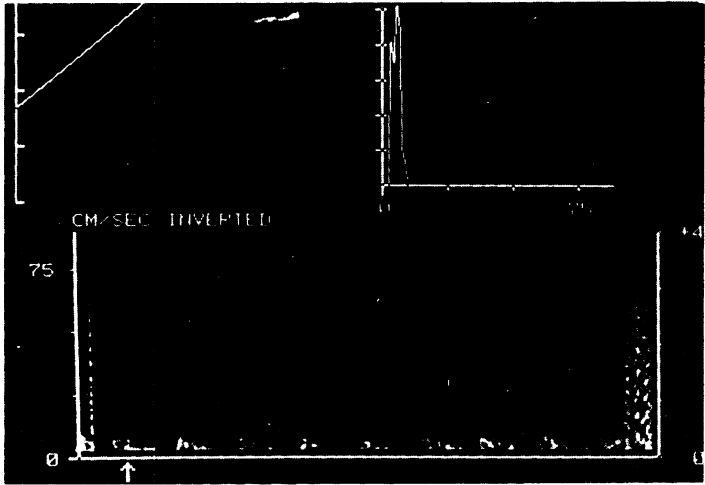


FIGURE 6 (See opposite page). Flow velocity measurement with pulsed Doppler ultrasound after intracavernous injection of 20 μg PGE₁: (A) velocity increase in the cavernous artery 1 min after the intracavernous injection; (B) greater velocity at 5 min; (C) velocity at 9 min after the injection, slightly less than that at 5 min. Before PGE₁ injection the cavernous artery was not detectable.

PGI₂ RESULTS. A flow signal could be detected only in monkey 2 after injection of 200 μg PGI₂. The maximal peak flow velocity of 15 cm/s occurred 24 min after the injection. The duration of the increase was between 31 and 47 min.

EXPERIMENT 4

With the aorta clamped, the cavernous bodies were perfused before and after injection of 20 μg PGE₁ in monkeys 9, 10 and 11. Two types of reaction were seen. In one monkey with a baseline plateau pressure of 75 cmH₂O, the recording rose off the scale 10 s after saline infusion was begun after PGE₁ injection. During this time the penis was fully erect, owing to venous occlusion (Fig 2). In the other two monkeys plateau pressures decreased to 44 cmH₂O (from 116 cmH₂O) and 46 cmH₂O (from 86 cmH₂O) respectively, 3 min after PGE₁ injection. No changes in systemic blood pressure occurred in any of the three.

DISCUSSION

Prostaglandin E₁ increases cavernous arterial blood flow. The fact that ultrasound signals could not be detected before injection but were easily detected after can be accounted for only by an increase in flow. Furthermore, intracavernous injection of PGE₁ leads to an increase in cavernous compliance (demonstrated by the change in plateau pressure during perfusion) owing to cavernous smooth muscle relaxation. The two types of responses seen with cavernous perfusion after PGE₁ injection are: a lowering of the plateau pressure from the baseline plateau; and an initial attenuation of the pressure increase with respect to the baseline plateau followed by a rapid increase in intracavernous pressure to off-scale levels (see Results). These two types of responses are not basically different, but represent a difference in the degree of smooth muscle relaxation. Moderate relaxation leads to a reaction of the first type; greater relaxation is accompanied by a closure of the venous drainage channels during perfusion, resulting in an increase in pressure to off-scale values. The degree and duration of this relaxation appear to be dose-dependent (eg 5 μg PGE₁ has a considerably shorter duration of action than 10 μg or 20 μg). This is similar to the finding of Stackl et al.¹² who reported a dose-dependent duration of action in men.

In humans, PGE₁ in doses up to 20 μg leads to a full erection in most impotent patients^{12,14}. In normal monkeys, however, the drug induces only some penile elongation, indicating only partial smooth muscle relaxation. The fact that venous occlusion occurred in only some of the monkeys reflects a difference in the degree of relaxation among the animals. The discrepant reaction between men and monkeys might result from a difference in the number of PGE₁ receptors in the cavernous tissue or, perhaps more importantly, a difference in the affinity of these receptors for PGE₁. Preliminary studies of PGE₁ receptors in our laboratory point to the importance of the latter. Furthermore, an effect of the ketamine anesthesia cannot be excluded.

PGE₁ is a natural constituent of many mammalian tissues²⁰, is rapidly metabolized after injection²¹, and apparently has fewer side-effects than papaverine after intercavernous injection^{11,12}. It is therefore an attractive alternative to papaverine.

We were unable to observe an increase in cavernous arterial flow after intracavernous injection of PGI₂. However, some considerations cast doubt on the results of our pulsed Doppler ultrasound studies: an increase in amplitude of arterial pulsations was superimposed on the intracavernous pressure recording in four of our eight monkeys; other investigators have reported that PGI₂ results in relaxation of cavernous arterial segments in the muscle bath¹⁶; in our study, penile shrinkage after intracavernous injection made measurements particularly difficult and possibly unreliable. Nevertheless, we found an increase in cavernous arterial flow in one of seven monkeys. Interestingly, this increase did not result in penile tumescence or erection, underscoring the importance of cavernous smooth muscle relaxation even in the early phase of the induction of erection. PGI₂ administration did not result in cavernous smooth muscle relaxation. The higher plateau pressures during cavernous perfusion after PGI₂ administration were invariably accompanied by penile shrinkage. These findings demonstrate that PGI₂ injection results in cavernous smooth muscle contraction and a lower cavernous compliance.

Additional studies of this drug could prove to be interesting. If the effects of PGI₂ on the cavernous artery could be measured more reliably *in vivo*, it may be possible to prove that arterial dilation cannot induce an erection if cavernous compliance is not increased at the same time. Our study shows that PGI₂ causes a decrease in cavernous compliance and shrinkage of the penis. As compared with the normal flaccid state, this shrinkage can be accounted for by increased myogenic tone. In the flaccid penis, the tone of the cavernous smooth muscles is maintained between full relaxation and full contraction. Hyperinvolvement of the penis on the basis of increased myogenic tone has previously been described in the rabbit after transection of the sympathetic chains²².

In conclusion, we found that PGE₁ acts *in vivo* via cavernous smooth muscle relaxation and an increase in blood flow in the cavernous artery. The degree and duration of these effects are dose-dependent. Venous outflow obstruction was found only in approximately one third of the monkeys studied.

With PGI₂ we did not observe an increase in cavernous arterial blood flow. A decrease in the cavernous compliance, however, was obvious. In contrast to PGE₁, PGI₂ appears not to be helpful in the diagnosis and treatment of impotence.

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