Effects of Prostacyclin (PGI₂), 6-oxo-PGF₁α and PGE₂ on Sympathetic Nerve Function in Mesenteric Arteries and Veins of the Rabbit In Vitro

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SUMMARY Prostacyclin is the principal product of prostaglandin (PG) endoperoxide (PGH₂) metabolism in rabbit mesenteric arteries and veins, as assessed by synthesis of 6-oxo-PGF₁α. Formation of PGE₂, PGD₂, PGF₂α, and C₁₇-hydroxyacid of PGH₂ (HHT) were also detected but arose probably from non-enzymic decomposition of PGH₂. The effects of prostacyclin (PGI₂), 6-oxo-PGF₁α and PGE₂ on sympathetic nerve function have been studied, using rabbit mesenteric arteries and veins in vitro. In mesenteric arterial strips, prostacyclin, when administered or when synthesized endogenously, attenuates contractions caused by electrical field stimulation of intramural nerves by reducing arterial responsiveness to the released norepinephrine. In veins, prostacyclin also diminishes output of the transmitter. In arteries and veins, 6-OXO-PGF₁α did not affect the output of transmitter or the contractions induced by exogenous norepinephrine. In arteries and veins, PGE₂ inhibited the output of adrenergic transmitter caused by nerve stimulation and was more active than prostacyclin. In arteries, PGE₂ reduced the contractions caused by added norepinephrine but in veins, PGE₂ augmented the effects. Thus, in mesenteric arteries and veins of rabbits, endogenous prostacyclin could normally act to oppose sympathetic nerve function. The predominant action in arteries is to attenuate smooth muscle responsiveness to the released transmitter, rather than to reduce adrenergic transmitter output. In veins, dulling of nerve function could additionally be brought about by a reduction in transmitter release. (Hypertension 1: 309-315, 1979)

KEY WORDS • prostacyclin (PGI₂) • adrenergic neurotransmission • 6-oxo-prostaglandin F₁α • mesenteric arteries • prostaglandin E₂ • mesenteric veins • in vitro • rabbit

PROSTAGLANDINS, when formed in blood vessel walls, may act, either locally or after release into the circulation, to alter peripheral vascular resistance. Thus, they could contribute to the maintenance of normal blood pressure. This activity could be due to the prostaglandins acting directly to modify smooth muscle tension and indirectly by opposing the vasoconstriction normally mediated by the sympathetic nervous system. Hedqvist has proposed that prostaglandins of the E-series counteract sympathetic nerve function in some blood vessels by reducing adrenergic transmitter release caused by nerve stimulation and by diminishing smooth muscle responsiveness to the released transmitter. However, it has been demonstrated that prostacyclin (PGI₂; (5z)-5,6-didehydro-9-deoxy-6,9α-epoxy-prostaglandin F₁) is the major intramurally generated prostaglandin that lowers blood vessel tone. Prostacyclin relaxes arterial strips in vitro and lowers arterial blood pressure by vasodilatation. It is the most potent known inhibitor of platelet aggregation. Prostacyclin is unstable in water and rapidly decomposes to 6-oxo-PGF₁α, a stable but considerably less active substance. In view of the discovery of prostacyclin we have retested Hedqvist's proposal by studying the effects of prostacyclin and 6-oxo-PGF₁α on the output of adrenergic transmitter and on vascular responsiveness to norepinephrine using rabbit mesenteric arteries in vitro.

Venous tension can also profoundly affect blood pressure through alterations in the return of blood to the heart with consequent modification of cardiac output. We have therefore investigated the effect of PGI₂ on sympathetic nerve function, using mesenteric veins. The results obtained were compared with those produced by PGE₂, which, before the discovery of prostacyclin, was thought to be a primary vascular prostaglandin. We have confirmed that prostacyclin and not PGE₂ is the principal prostaglandin synthesized from the endoperoxide PGH₂ (15-hydroxy-9α,11α-peroxidoprosa-5,13-dienoic acid) in mesenteric arteries and veins of the rabbit. The results described here in detail supplement a preliminary report concerned with some of the qualitative effects of prostacyclin and PGE₂ on sympathetic nerve function in arteries. The findings support our earlier proposition that in arteries, attenuation of sympathetic nerve function by prostacyclin is more likely
to be due to a lowering of arterial sensitivity to the
adrenergic transmitter than to its ability to reduce the
output of the transmitter from nerve endings. We have
now found that prostacyclin can reduce transmitter
output in veins.

Methods and Materials

Male New Zealand white rabbits weighing 2-3 kg
were killed by cervical dislocation. The major
mesenteric artery was carefully dissected from its
origin at the aorta and the mesenteric vein was also
carefully removed.

Prostaglandin Production

Arteries and veins from six rabbits were cleaned of
connective tissue and then cut into small rings. Rings
of either type of tissue were pooled and then separated
into two groups each comprised of approximately 180
mg of tissue so that control and test groups contained
tissue arising from the same animal. To each group
was added 1 ml tris buffer (50 mM, pH 7.5). One
group of arteries and one of veins were boiled for 2
minutes to destroy tissue enzyme activity and were
used as controls. We prepared (1-14C)-prostaglandin
H2 (specific activity 6.3 mCi/mmoles) from (1-3H)-
arachidonic acid (specific activity 60 mCi/mmoles)
using an acetone pentane preparation of ram seminal
vesicles as the enzyme source. We added 1.6 ìg (1-
C) prostaglandin H2 to each group of blood vessel rings
and continued incubation for 3 minutes at 20°C. En-
doperoxide metabolism was terminated by adding 3
ml of ice-cold acetone. This mixture was shaken and
subsequently centrifuged to precipitate the tissue.
After decanting the aqueous-acetone layer, neutral
lipsids were extracted using hexane. The remaining
aqueous-acetone was adjusted to pH 4 with 0.5 M
citric acid and extracted with chloroform (two
volumes of 2.5 ml). The combined chloroform layers
were dried under nitrogen and the residue dissolved
in chloroform-methanol (2:1 v/v, 100 ml) and this solution
was applied to a thin-layer chromatography plate
(Uniplate, precoated with silica gel G 0.250 µm)
together with authentic PGF1α, PGD2, PGF2α and 6-
oxo-PGF1α. The plate was developed in the organic
phase of ethyl acetate, trimethylpentane, acetic acid
and water (in ratio of their respective volumes
110:50:20:100). Areas of radioactivity on the plate
were located with a Panax RTLS-1A radiochro-
matogram scanner.

Sympathetic Nerve Function

Arteries and veins were cut spirally (each measuring
approximately 4 x 30 mm) and strips suspended in a
water-jacketed glass container tying one end to a glass
hook and connecting the other by thread to a force-
displacement transducer (Grass FT03C Grass Instru-
ment Co., Quincy, MA), to allow recording of
isometric tension. During the experiment a resting
tension of 1-1.5 g was applied to the tissue, this having
previously been found to be optimal for contractile ac-
tivity. Blood vessel strips were superfused at 3 ml/min
with solution comprised of: NaCl, 118.0 mM; KCl,
4.7 mM; MgCl2, 1.2 mM; Na2HPO4, 1.0 mM; CaCl2,
2.6 mM; NaHCO3, 25.0 mM; glucose, 11.1 mM; and
ascorbic acid, 0.1 mM. Before superfusion, the solu-
tion was gassed with oxygen (95%) and CO2 (5%) and
warmed to 37°C.

To allow detection of adrenergic transmitter output,
arteries and veins were bathed in superfusion fluid
containing 10−5 M (D- or L) norepinephrine (3.4
Ci/mmoles) for 1 hour to load tissue amine stores
radioactively. Thereafter, strips were superfused
for 45 minutes with a solution free of radioactive
norepinephrine and, in experiments with arteries, the
fluid contained cocaine (3 x 10−6 M) and (±) nore-
metanephrine (10−5 M) to inhibit norepinephrine-
uptake mechanisms and thereby increase the outflow
of radioactivity (our unpublished observations). Elec-
trical field stimulation of nerve endings was ac-
complished with two parallel platinum electrodes,
placed one on either side of the tissue, and a
stimulator (Grass S88) set to deliver at 14-minute in-
tervals trains of 300 rectangular monophasic pulses
of supramaximal voltage, 1.5 msec duration and 2 Hz.
Superfusate was collected during 2-minute periods
and the radioactivity in 1-ml aliquots determined in a
Packard Liquid Scintillation Spectrometer, using
Biofluor (New England Nuclear Corp.) as counting
medium. Quenching was corrected by use of internal
standards. Release of radioactivity by electrical field
stimulation of intramural nerves was taken as an in-
dex of adrenergic transmitter release. Output of
radioactivity evoked by electrical stimulation was
calculated as fractional output per shock using the
method of Stjärne and Brundin.10 Fractional output
per shock was calculated for each period of stimula-
tion after determining the evoked rise in efflux of
radioactivity and dividing the value obtained by the
total amount of radioactivity contained in the tissue
at the start of the stimulation period; the quotient was
then divided by 300 (the number of shocks applied).
Total tissue radioactivity present at the beginning of
each stimulation period was determined by adding
together all the values of radioactivity (dpm) subse-
sequently obtained in samples collected up to the end
of the experiment and the radioactivity remaining in the
tissue 14 minutes after the last stimulation period. The
radioactivity remaining in the tissue was released for
counting by immersing each blood vessel in digestant
fluid. The digestant comprised of Triton 405 nonionic
detergent (50 ml) and methanol (150 ml). Release of
radioactivity was facilitated by heating the mixture
and tissue to 70°C for 2 hours. After the mixture was
cool, 0.5 ml of concentrated HCl was added. One-ml
aliquots of the digested mixture were transferred to
vials and Biofluor Liquid Scintillant (10 ml) was
added before measurement of the radioactivity.
Preliminary experiments, using the method of Graefe
et al.11 to separate norepinephrine from its metabolites
by means of alumina columns, showed that, of the
radioactivity released by nerve stimulation, ap-
proximately 90% appeared in the fraction correpond-
ing to authentic norepinephrine. This indicated that the radioactivity released is comprised substantially of unchanged norepinephrine. Increases in the output of radioactivity caused by electrical stimulation were reduced to approximately 10% or lower by either tetrodotoxin (10^4 M) or bethanidine (10^6 M) added to the superfusion fluid to block adrenergic neurones (our unpublished observations). This indicated that the radioactivity released originated almost entirely from adrenergic nerves. Alterations in sympathetic nerve function in blood vessels brought about by agents changing the responsiveness of the vascular smooth muscle to the released transmitter, were assessed by looking for differences in the size of contractions produced by exogenous norepinephrine (1–2 μg producing approximately 40–60% of the maximal response) added to the superfusion fluid at intervals of 6 minutes.

Prostacyclin was dissolved in 50 mM tris buffer (pH 8.4) immediately before the start of infusions. Using a roller pump (Delta, Watson Marlow) prostacyclin was diluted 40 times before addition to the superfusion fluid and thereafter it was in contact with superfusion fluid for 1 minute to allow warming to 37°C. The potency of prostacyclin used in this way was checked daily by assay for its ability to inhibit platelet aggregation.

Materials

We obtained the following materials for our experiments: sodium prostacyclin, PGD_2, 6-oxo-PGF_1α (N. Whittaker, Wellcome Research Laboratories); PGE_2, PGF_2α (Cambrian Chemicals); (−)-norepinephrine bitartrate, (±)-normetanephrine (Sigma); indomethacin (Merck, Sharp and Dohme); cocaine hydrochloride (McFarlane-Smith); (−)-7-3H-norepinephrine hydrochloride, [1-14C]-arachidonic acid (Radiochemical Centre, Amersham); C_17-hydroxyacid of PGH_2 (HHT) was obtained from decomposition of PGH_2 and its chemical structure confirmed by using gas chromatography-mass spectrometry.

Results

Prostaglandin Production in Arteries and Veins

Radiochromatogram scans are shown in figure 1 for arteries (upper panel) and veins (lower panel). The solid lines correspond to products formed by normal tissue (Test) and the broken lines correspond to tissue that had been boiled to destroy enzymes concerned with prostaglandin metabolism (Blank). In both arterial and venous tissue the amount of 6-oxo-PGF_1α produced was similar. This prostaglandin was not present in detectable quantities in boiled tissues indicating that endoperoxide transformation leading to 6-oxo-PGF_1α formation was enzymic. As 6-oxo-PGF_1α is the stable degradation product of prostacyclin, the latter agent is evidently the principal metabolite of the endoperoxide formed by these blood vessels. Both PGE_2 and HHT were also detected but

The effects of indomethacin, prostacyclin and PGE_2 on the output of radioactivity and blood vessel tension caused by successive periods of field stimulation of sympathetic nerves in a single experiment are shown in figure 2, left, for an arterial preparation and in
**Figure 2.** Fractional $^3$H-output/shock ($\times 10^4$) and vascular smooth muscle contractions caused by successive periods of electrical field stimulation at 14-minute intervals using an artery (left panel) and a vein (right panel). Agents were added to the superfusion fluid for periods indicated by the horizontal bars. During control periods superfusion fluid was added. Fractional $^3$H-output/shock was used as a measure of adrenergic transmitter release evoked by electrical stimulation of intramural nerves and was calculated as described in Methods. (Figure 2 (left panel) is reprinted from: Armstrong JM, Thirsk G: Effects of prostacyclin (PGI$_2$), 6-oxo-prostaglandin F$_{1\alpha}$ and prostaglandin E$_2$ on sympathetic adrenergic nerve function in rabbit mesenteric arteries in vitro. In Presynaptic Receptors. A satellite meeting of the 7th International Congress of Pharmacology, 1978. In press, with permission of the publisher.)

**Figure 3.** Graphs relating inhibition of $^3$H output/shock (left panel) or contractions to exogenous norepinephrine (right panel) to the concentration of either prostacyclin or PGE$_2$ added to superfusion fluid containing indomethacin ($5 \times 10^{-6}$M) in four mesenteric arteries.

Figure 2, right, for a venous preparation. Shown in Figure 3, left, are the graphs drawn from pooled data using arterial preparations, relating the mean percentage inhibition of $^3$H-output to the concentration of prostacyclin or PGE$_2$ used, in the presence of indomethacin ($5 \times 10^{-6}$M). Shown in Figure 3, right, are the graphs of the inhibitory effects of prostaglandins on contractions caused by exogenous norepinephrine.
also in the presence of indomethacin. Analogous graphs for venous preparations are shown in figure 4, left, for \(^{3}H\) output and in figure 4, right, for contractions caused by norepinephrine.

**Arterial Preparations**

Figure 2, left, shows that, after addition of indomethacin (5 × 10\(^{-6}\)M) to the superfusion fluid, contractions induced by nerve stimulation were increased by 60–70% and that the basal tension was increased by approximately 0.1 g. At the same time, output of radioactivity to nerve stimulation was unchanged. In this experiment, prostacyclin lowered the basal tension previously increased by indomethacin and decreased contractions, caused by nerve stimulation, by approximately 70%; radioactivity, released concomitantly, was unaffected. Fourteen minutes after removal of the prostacyclin from the superfusion fluid, contractions produced by electrical stimulation returned to the size recorded immediately before the addition of prostacyclin. In the presence of indomethacin (5 × 10\(^{-6}\)M), addition of PGE\(_2\) (10\(^{-6}\)M) decreased the accompanying output of radioactivity evoked by nerve stimulation. Restoration of both responses to nerve stimulation was slower in the case of PGE\(_2\) compared with PGI\(_2\). The concentration of PGE\(_2\) required for a threshold reduction in the output of radioactivity from four arteries was within the range of 10\(^{-8}\)M to 10\(^{-6}\)M (fig. 3, left). The magnitude of the inhibition increased with the concentration of PGE\(_2\) used and achieved 90–100% reduction with 10\(^{-6}\)M. The magnitude of the reductions in output of radioactivity to nerve stimulation, produced after PGI\(_2\), were not proportional to the concentration used (10\(^{-6}\)M to 10\(^{-4}\)M). Prostacyclin was highly effective in diminishing responses to exogenous norepinephrine, whereas PGE\(_2\) was less active (fig. 3, right). The concentrations of prostacyclin required for a threshold effect in four preparations were less than 10\(^{-6}\)M and those for PGE\(_2\) approximately 10\(^{-5}\)M. After 10\(^{-5}\)M prostacyclin, contractions to exogenous norepinephrine were reduced by 90% of their initial control values. In contrast, after PGE\(_2\) (10\(^{-4}\)M), contractions induced by norepinephrine were reduced by only 50% of the control values.

Addition of indomethacin (5 × 10\(^{-6}\)M) to the superfusion fluid was followed in each of four preparations by augmentation of contractions to exogenous norepinephrine from initial control responses (100%) to 171.2 ± 8.0% (p < 0.001).

**Venous Preparations**

Figure 2, right, shows that after indomethacin (5 × 10\(^{-6}\)M) had been included in the superfusion fluid, contractions produced by nerve stimulation were essentially unchanged, whereas the associated release of radioactivity was increased by 25–30%. In the presence of indomethacin (5 × 10\(^{-6}\)M), addition of prostacyclin (10\(^{-5}\)M) to the electrolyte was followed by reductions in both overflow of radioactivity and the size of contraction to nerve stimulation. Stimulation-evoked output of radioactivity rapidly returned to control values after omission of the prostacyclin. Thereafter, addition of PGE\(_2\) (10\(^{-6}\)M) was followed by a substantial reduction (85%) in overflow of radioac-
tivity and a reduction of 50% in the accompanying contraction. At the same time, PGE₃ (10⁻⁴M) appeared to increase the resting venous tension by 20%. Restoration of the output of radioactivity and contractions produced by nerve stimulation occurred 30 minutes after omission of PGE₃. In groups of four preparations, the concentration of PGE₃ needed for a threshold reduction in output of radioactivity was less than 10⁻⁴M and that for prostacyclin was approximately 10⁻⁴M (fig. 4, left). We found that PGE₃ was more effective than prostacyclin in reducing output of radioactivity at concentrations of 10⁻⁴M to 10⁻³M but that the two substances were equally active at 10⁻²M.

After indomethacin (5 × 10⁻⁴M), contractions to exogenous norepinephrine were not substantially different from initial values (P > 0.05, n = 4). Thereafter both prostaglandins altered contractions caused by exogenous norepinephrine. PGE₃ (10⁻⁴M) augmenting response by 30% whereas PGI₂ (10⁻⁴M) reduced contractions by 30% (fig. 4, right).

We found that 6-oxo-PGF₆α (10⁻⁴M to 10⁻³M) did not cause any detectable effect on either the radioactivity released or contractions evoked by nerve stimulation in groups of four arteries or four veins; nor did this substance alter basal tension developed by the preparations. None of the prostaglandins used altered the basal output of radioactivity from arterial or venous strips in the absence of electrical field stimulation.

**Discussion**

The dienoic prostaglandin endoperoxides such as PGH₂ are essential intermediates in the formation of PGE₃, PGD₂, PGF₂α, and thromboxane A₂. Moreover, prostacyclin is a principal metabolite of arachidonic acid, produced by all blood vessels so far examined. We have now found that prostacyclin is the major metabolite of the endoperoxide PGH₂ produced in mesenteric arteries and veins of the rabbit in vitro. The other substances detected, PGE₂ and HHT, are probably chemical decomposition products of PGH₂ because they do not need viable enzymic mechanisms present for their formation. Recently, Skidgel and Printz have reported that arterial tissue of the rat produces more 6-oxo-PGF₁α (and thus PGI₂) from exogenous PGH₂ than veins, at all protein concentrations tested. However, our results demonstrate that mesenteric arteries and veins of the rabbit synthesize similar amounts of 6-oxo-PGF₁α. Nevertheless, our findings support the conclusion of Armstrong et al. and of Skidgel and Printz that prostacyclin synthesis is the predominant prostaglandin enzymic activity manifest in blood vessels.

The finding that prostacyclin and not PGE₃ is the principal prostaglandin produced by certain blood vessels necessitates a re-interpretation of Hedqvist's hypothesis concerning the operation of a negative feedback mechanism for endogenous prostaglandins of the E-series. This hypothesis proposes that PGEs, mobilized by sympathetic nerve activity, attenuate adrenergic transmitter output evoked by nerve stimulation and reduce smooth muscle responsiveness to the norepinephrine released. We now propose that in rabbit mesenteric arteries and veins, and perhaps in other blood vessels, prostacyclin and not PGE₃ should be considered as the principal candidate for such a role. This suggestion is supported by our observation that in both mesenteric arteries and veins prostacyclin is the major metabolite of endoperoxide metabolism. Moreover, in both types of blood vessels, exogenous prostacyclin lowered blood vessel contractions produced by nerve stimulation and by exogenous norepinephrine. The magnitude of this reduction was largely proportional to the concentration tested. The inhibitory effect of prostacyclin on blood vessel responsiveness is unlikely to be due to its degradation product 6-oxo-PGF₆α because the latter was inactive.

Our finding that prostacyclin reduced contractions of mesenteric veins produced by 1–2 μg norepinephrine is at variance with that of Herman et al. who used saphenous veins of the dog. These workers showed that whereas prostacyclin (1.5 × 10⁻⁴M) significantly reduced the response of the saphenous veins to low doses of norepinephrine (1 to 5 × 10⁻⁵M) it did not alter contractions induced by concentrations of the amine that were similar to those used in our study (1 to 5 × 10⁻⁴M). Moreover, our results show that prostacyclin inhibited adrenergic neurotransmission in mesenteric veins as evinced by a diminished output of radioactivity. In contrast, Herman et al. suggested that prostacyclin produced a dual effect, causing depression of smooth muscle responsiveness to norepinephrine and enhancement of the evoked release of adrenergic transmitter.

Our observation that prostacyclin inhibits contractions of rabbit mesenteric arterial strips evoked by nerve stimulation resembles that of Weitzell et al. who used rabbit pulmonary artery strips. However, in contrast to Weitzell et al., we failed to demonstrate that prostacyclin reduced the stimulation-evoked output of adrenergic transmitter. The differences occurring between the results of the present study and those of either Herman et al. or Weitzell et al. could be due to the considerable differences in the tissues used and the experimental conditions employed. In the present study, effects of prostacyclin were determined with indomethacin retained in the superfusion fluid to inhibit synthesis of endogenous prostaglandins that might otherwise modify sympathetic nerve function. Such effects would depend upon the type of the prostaglandins formed, the relative amounts produced and the potencies of their actions at both pre- and postsynaptic sites. In the case of mesenteric veins, PGE₂ was more active than prostacyclin in attenuating transmitter release and augmented blood vessel responsiveness. In the case of mesenteric arteries, only PGE₂ consistently reduced transmitter output but this prostaglandin was less active than prostacyclin in reducing vascular smooth muscle reactivity.

We have used indomethacin as a pharmacological tool to study the effects of endogenous prostaglandins on sympathetic nerve function and have assumed that...
such effects are a consequence of its capacity to inhibit prostacyclin production. This assumption is acceptable for the following reasons: 1) there is now overwhelming evidence that indomethacin, as with other aspirin-like drugs, can inhibit prostaglandin cyclooxygenase and thereby inhibit all prostaglandin production; 2) aortic, mesenteric and cerebral arterial tissues of the rabbit generate an unstable substance, which was formerly called prostaglandin X and was subsequently shown to be prostacyclin. Both the basal release of prostacyclin and the release stimulated with arachidonic acid was inhibited by previous treatment with indomethacin or by washing the tissue with a solution of indomethacin of concentration similar to that used in the present study (5 × 10^{-6}M). Moreover, indomethacin did not interfere with the metabolic conversion of endoperoxide to prostacyclin; 3) few other enzyme systems could be expected to be inhibited at the low concentrations of indomethacin needed for cyclooxygenase inhibition; and 4) in the present study, after indomethacin had been added to the superfusion fluid, effects on transmitter release and blood vessel responsiveness were usually in a direction opposite to that produced by exogenous prostacyclin. Our observation that endogenous or exogenous prostacyclin inhibited arterial contractions caused by nerve stimulation but did not attenuate transmitter release suggests that the major effect of this prostaglandin is likely to be at postsynaptic sites since there was little evidence of activity at arterial presynaptic neuronal sites. Moreover, the endothelium has been shown to possess a much greater synthetic capacity for prostacyclin than the adventitial or medial layers where the sympathetic nerve endings are located.

The apparent difference between arteries and veins in the susceptibility of their neurotransmission mechanisms to inhibition by prostacyclin is unexplained. However, analogous differences in the sensitivity among different vascular beds in animals of the same species, and in the same vascular bed among different species to the effects of prostaglandins have already been reported.

Thus, prostacyclin, when synthesized by blood vessel walls or when present in the blood, could modify sympathetic nerve function by diminishing the output of adrenergic transmitter or attenuating the smooth muscle responsiveness to the norepinephrine released. However, the magnitude of the effect at pre- or postsynaptic sites appears to depend upon the vascular tissue being studied.

Acknowledgment

We should like to thank Christine Brook for excellent technical assistance.

References


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Hypertension. 1979;1:309-315
doi: 10.1161/01.HYP.1.3.309

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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