LETTER TO THE EDITOR

ROLE OF PROSTAGLANDINS IN HYPOTENSION FOLLOWING PRESSOR RESPONSE TO INTRAVENOUS INFUSION OF NORADRENALINE IN DOGS

Sir,

(Received on October 14, 1985)

It was observed that even with continous iv infusion at 40 *μg/kg/min* of adrenaline (ADR) (1) or noradrenaline (NA) in dogs (8) the blood pressure was elevated only for sometime but later it declined. In light of reports that NA causes release of prostaglandins (PGs)(7) from kidney and spleen the role of PGs in the hypotension following initial pressor effect during NA iv infusion were studied in dogs with the kidneys and spleen removed or pretreated with indomethacin an inhibitor of PG synthesis.

In 17 dogs (7-11 *kg*) under pentobarbitone anaesthesia (40 *mg/kg*, iv) carotid blood pressure was recorded with mercury manometer. Splencetomy and bilateral nephrectomy were done through an anterior abdominal incision 30 min before NA infusion 10 *μg/kg/min* (0.3 *ml/min*) through femoral vein. Indomethacin (10 *mg/kg*) was given as single iv injection 15 min before start of infusion. (—) Noradrenaline-bitartrate (Fluka), (—) adrenaline bitartrate (Boehringer) and indomethacin (Fabrica Italina Sintetici SPA) were used; doses refer to the salts.

The blood pressure rose immediately by about 100 to 120 mm Hg on starting NA infusion. However, the rise of blood pressure was not sustained and blood pressure progressively declined, despite continued infusion, reaching the preinfusion level in 34 to 62 min. Blood pressure slowly declined further ending in death after some time. Table I gives the duration of the pressor effect and the survival time.

Removal of either spleen or both kidneys (one expt. each) delayed the decline of blood pressure and increased the duration of the pressor effect and survival time (Table I). In 5 other experiments spleen and both kidneys were removed when there was an increase ($P < 0.05$) in the duration of the pressor effect. The average survival time also increased from 155.5 to 238.8 min but this was not statistically significant. This suggests that

spleen and kidneys could have contributed partly to the decline of blood pressure that occurred during NA infusion.

TABLE I : Effect of infusion of NA (10 $\mu g/kg/min$, iv) on blood pressure and the survival time of pentobarbitone anaesthetized dogs.

	No. of experiments	*Mean duration of pressor effect in min±SEM*	*Mean survival time in Min ±SEM*
i. Control	4	50 ±5.9	155.5±25.1
ii. After splenectomy	1	95	200
after nephrectomy	1	85	210
after splenectomy and nephrectomy	5	130.6±29.6*	238.8±12.3^{NS}
iii. Pretreatment with indomethecin	6	78.6±7.8*	212.5±32.7^{NS}

*Differs significantly from control ($P<0.05$, t-test) : NS; difference not significant.

In 6 dogs which were pretreated with indomethacin, the duration of pressor effect was increased ($P < 0.05$). The average survival time was also increased from 155.5 to 212.5 though this was not statistically significant.

Failure of continous infusion of NA to maintain blood pressure could be due to reflex changes in cardiovascular system, changes in receptor sensitivity, reduced perfusion of vital organs or release of vasodilator substances. PGs are known to be released in response to nerve stimulation as well as exogenous NA injection in cat spleen (5, 2) in rabbit kidneys (10, 3) rabbit mesenteric vessels (6) and their release is blocked by inhibitors of PG synthesis like indomethacin. Vasodilator action of PGs is well documented in animals and also in man (9). PG E_2 inhibits renal vascular response to renal nerve stimulation and to a lesser extent exogenous NA in the dog and rabbit Kidney (4). Removal of kidney, spleen or both in our experiments prolonged the pressor effects of NA suggesting that PG release from these organs could contribute partly to the hypotensive phase of NA infusion. This was supported by our finding that prior treatment with indomethacin delayed the decline of the pressor response to infusion of NA. Ferriera *et al.* (2) found that inhibition of PG synthesis with indomethacin resulted in augmentation of capsular and vascular responses to nerve stimulation, and to injected NA and angiotensin in cat spleen preparation. They suggested that antagonism of effects of NA

on smooth muscle by PGs is atleast as important a homeostatic mechanism as is the reduction of release of NA by them.

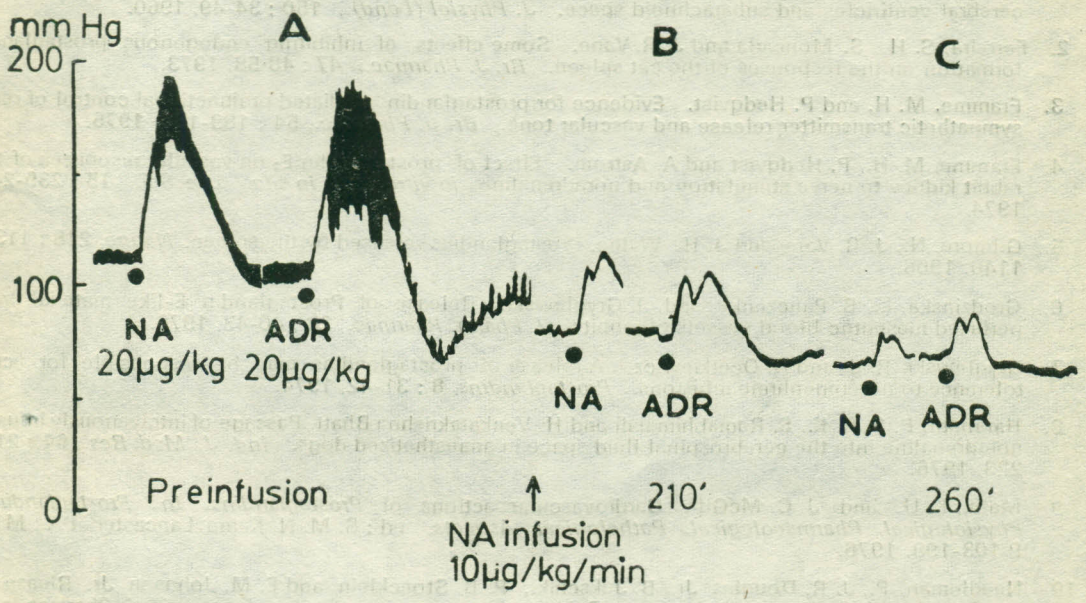

Fig. 1. Response of blood pressure to NA and ADR before (in A) and during iv infusion of NA at 210 min (in B) and 260 min (in C). Note the progressive fall in resting blood pressure despite continuous NA infusion (which initially raised BP to 200 mm Hg).

Present experiments showed a reduced sensitivity of alpha receptors during hypotensive phase (Fig. 1). Tachyphylaxis is generally described for bolus injections of indirectly acting sympathomimetic amines but not to NA. The progressive loss of pressor effect can be explained partly by the attenuated sensitivity of alpha receptors, but not the hypotension. It is therefore presumed that hypotension following the pressor response to continuous iv infusion of NA could be in part due to release of PGs and to reduced sensitivity of alpha receptors.

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