Stabilization of endothelial lining and decrease in circulating endothelial cells – one mechanism underlying the clinical action of PGE₁?

It has been demonstrated that hyperlipidaemia and smoking (Velican, 1978) cause increased endothelial turnover which is nicely reflected by a rather simple test for circulating endothelial cells (Davis *et al.*, 1987) originally described by Hladovec (1978). Recent studies have proven the endothelial nature of these circulating cells (Davis *et al.*, 1985). We assessed the effect of treatment for 5 days with prostaglandin (PG) E₁ on the amount of circulating endothelial cells and on the platelet half-life ($t_{1/2}$) in patients suffering from peripheral vascular disease (PVD).

In this study 21 patients were infused intravenously with PGE₁ (α -cyclodextrin PGE₁, Sanol Schwarz GmbH, Monheim, FRG) at a rate of 20 ng kg⁻¹ min⁻¹ for 6 h daily for 5 consecutive days. Platelet $t_{1/2}$ was determined after radiolabelling of autologous platelets (Sinzinger *et al.*, 1984) using ¹¹¹indium-oxine-sulphate before and after therapy. Circulating endothelial cells were quantified before and at the end of therapy as well as 1 week and 1 month after. The estimation of circulating endothelial cells (CEC) was performed as follows: briefly, citrated blood (3.8% sodium citrate) was sedimented for 10 min and centrifuged at 150g for 7 min to obtain platelet rich plasma (PRP). Platelets were removed by an overdose of ADP of at least 50 μ M. After removing the platelets by a further centrifugation step, the remaining cellular elements were circulating endothelial cells and these were pelleted by a final centrifugation for 10 min at 1000g. The pellet was resuspended in Plaxan, stained and counted in a

Bürker-Türk chamber; the number of CEC is given per μ l.

Blood from smokers and patients with hyperlipoproteinaemia contained more endothelial cells than did that of PVD-patients without risk factors (Table 1). PGE₁ caused a drop in CEC as well as a significant ($P < 0.01$) prolongation in platelet $t_{1/2}$ in each of the three groups ($P < 0.01$).

The finding of a decrease in CEC paralleled by an increase in platelet $t_{1/2}$ suggests a beneficial action of PGE₁ at the endothelial level. This may be due to cytoprotection and could be one mechanism for the decreased thrombogenicity (Sinzinger *et al.*, 1987) seen in man.

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Table 1 $t_{1/2}$ and CEC after a 5 days therapy with 20 ng PGE₁ i.v. (mean $\pm$ s.d.)

		Prevalue	End of therapy	After 1 week	After 1 month
PVD	$t_{1/2}$ (h)	77 $\pm$ 7	82 $\pm$ 6*	—	—
(n = 11)	CEC (n μ l ⁻¹)	7 $\pm$ 4	2 $\pm$ 1*	3 $\pm$ 2*	3 $\pm$ 1*
+ Smoking	$t_{1/2}$ (h)	69 $\pm$ 8	77 $\pm$ 7*	—	—
(n = 4)	CEC (n μ l ⁻¹)	35 $\pm$ 14	21 $\pm$ 9*	24 $\pm$ 7*	26 $\pm$ 9*
+ HLP	$t_{1/2}$ (h)	71 $\pm$ 7	78 $\pm$ 5*	—	—
(n = 6)	CEC (n μ l ⁻¹)	18 $\pm$ 7	10 $\pm$ 4*	9 $\pm$ 3*	13 $\pm$ 8*

* $P < 0.01$ (vs prevalue, Student's *t*-test)

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The effect of atropine on heart-rate: a comparison between two ethnic groups

The effect of atropine on heart-rate may differ greatly between individuals at equivalent doses (Crawford, 1923). Atropine also has varying effects on the heart-rate, depending on the age of the subject (Nalefski & Brown, 1950). Vagal tone is thought to be the most important determinant of effective dose (Chamberlain & Turner, 1967) as a definite negative correlation exists between basal resting heart rate and the dose required for complete parasympathetic blockage (Kauf, 1926). The dose of atropine sufficient to cause striking cardiac acceleration in an untrained individual may be relatively ineffective in an athlete (Chamberlain & Turner 1967). A difference in response to atropine in Caucasian and Negroid races has been described (McGuigan, 1921; Paskind, 1921). Paskind (1921) reported that the initial bradycardia after parenteral administration of atropine does not occur in the American Negro at doses which cause a bradycardia in matched white controls. The initial bradycardia only occurs transiently at relatively much higher doses of atropine. This decreased susceptibility to the bradycardia effects of atropine cannot be explained on pharmacokinetic grounds.

After rapid intravenous administration of atropine, a second episode of bradycardia occurring 1 h after administration has been described (Meyer *et al.*, 1986; Rudolf, 1924). In the present study, the effect of intravenous atropine 0.5 mg, on the heart-rate of eight white male volunteers was compared with the effect on 10 Venda males. The trial was single-blind, placebo controlled and ethically approved. There was no significant difference in the average age of the two groups of volunteers, and volunteers remained fasting and supine during the trial period of 5 h. Pulse rate was counted from the QRS complexes on ECG tracings (lead

2) taken continuously for the first 4 min after rapid intravenous administration of atropine 0.5 mg, and thereafter from 30 s tracings taken at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min. For statistical analysis the differences between the atropine and placebo values were calculated to determine the effect of atropine on each group. The absolute change in pulse rate (i.e. pulse rate at specific time – base line pulse) at each time-interval was further calculated and the two groups compared with each other by means of an analysis of variance, *P* values < 0.05 being regarded as significant throughout.

There was no difference statistically in the basal pulse rate between the two groups (Whites and Vendas 65 and 64 respectively).

After the administration of placebo there was no significant change in the pulse rate during the trial session.

After the administration of atropine 0.5 mg, there was a significant difference in heart-rate reaction between the Venda and White volunteers (Figure 1). The White volunteers developed a slight, statistically insignificant decrease in heart-rate (mean of 2 beats min^{-1}) while the Venda group responded with a mean increase of 8 beats min^{-1} . At 15 min the White volunteers had a slight increase in pulse rate of 4 beats min^{-1} , while the Vendas had a significant increase of 11 beats min^{-1} . The bradycardia developing at 150 min was significantly different between the two groups (Whites a mean decrease of 1 beat min^{-1} and Vendas a mean decrease of 12 beats min^{-1}).

Of the White volunteers, five developed early heart-arrhythmias; four developed A-V dissociation within the first 4 min and one developed downward displaced ST-segments. All the arrhythmias were of short duration and not present on the ECG tracings after 15 min. Of the