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Plasma Adrenaline: Relations to Blood Pressure, Blood Platelet Function and Blood Lipids in Essential Hypertension

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Introduction

For various reasons plasma catecholamines should be measured in arterial blood when comparing hypertensive and normotensive groups (1, 2). Measurements of plasma catecholamines in peripheral venous blood may conceal important hypertensive-normotensive differences (2). Plasma catecholamines seem to be subjected to a peripheral arterial-venous fractional extraction of approximately 50%. Thus, arterial adrenaline represents the effective adrenaline concentration to which the tissues are exposed. Besides, plasma noradrenaline in peripheral venous blood mainly represents local release related to skeletal muscle sympathetic tone which seems unchanged in essential hypertension (3).

Heart Rate and Plasma Catecholamines in Essential Hypertension

Increased heart rate in essential hypertension may be caused by an increase of sympathetic tone, decrease of parasympathetic tone, or both (4). According to our observations (1, 2) concomitantly increased heart rate and arterial catecholamines may be encountered in essential hypertension (Fig. 1). Such correlations observed between blood pressure, heart rate and arterial catecholamine concentrations are compatible with an increase of sympathetic tone possibly combined with less parasympathetic cardiac inhibition playing a causative role in the genesis of essential hypertension. If, however, another pathophysiological mechanism than altered autonomic function was operating, cardiac frequency would have been unchanged or even depressed by activated baroreflexes.

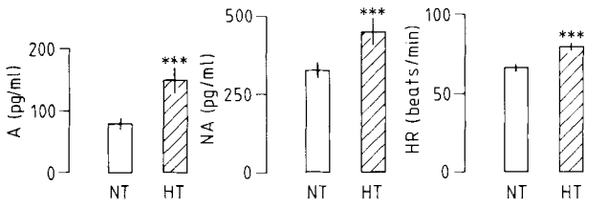

Fig. 1. Resting arterial plasma catecholamines and heart rate (means ± SE) in 50-year-old men, normotensive (NT) controls (open bars; blood pressure (BP): 132 ± 3/83 ± 2 mmHg; n = 19) and untreated patients with sustained essential hypertension (HT: hatched bars; BP: 176 ± 4/115 ± 2 mmHg; n = 20). A: adrenaline; NA: noradrenaline; HR: heart rate. ***, $p < 0.001$. Data from Kjeldsen et al. (1).

Plasma Adrenaline and Blood Platelet Function in Essential Hypertension

In several studies we have related increased platelet function to raised sympathetic adrenergic tone in essential hypertension. A positive correlation was found between increased arterial plasma adrenaline and plasma concentration of the platelet release reaction marker beta-thromboglobulin (5). When a small, physiological dose of adrenaline was infused to essential hypertensive subjects (6), their platelet count, platelet size and plasma concentration of beta-thromboglobulin increased more than in normotensive control subjects (Fig. 2). Thus, hypertensive blood platelets seem to possess hypersensitivity to adrenaline. The explanation may be found in the lack of a rapid alpha$_2$-adrenoceptor desensitizing mechanism in hypertension (7).

Plasma Adrenaline and Blood Lipids

The enzyme lipoprotein lipase is involved in the formation of high-density lipoprotein (HDL)-like particles through catebolism of triglyceride-rich very low-density lipoprotein (VLDL) particles (8). Hence, the finding of an inverse corre-

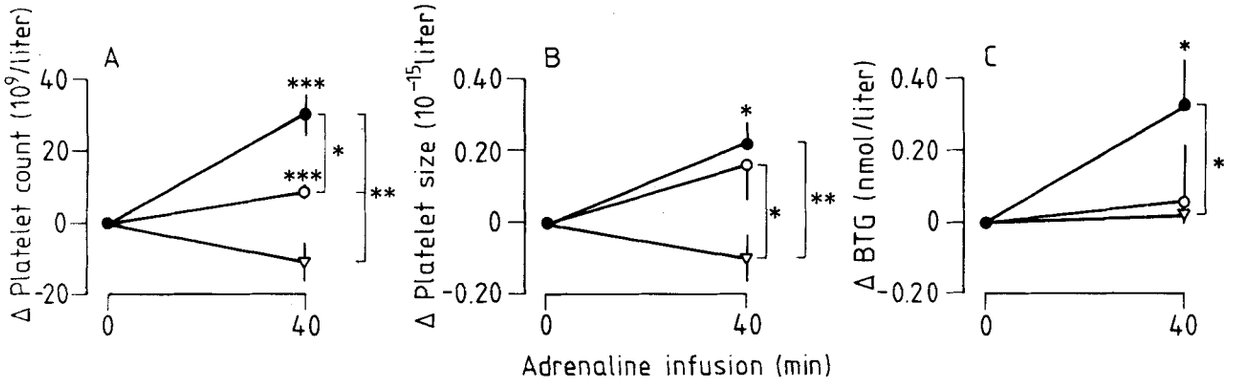

Fig. 2. Effect of i.v. adrenaline infusion on (A) platelet count; (B) platelet size and (C) plasma concentrations of beta-thromboglobulin (BTG) in 40-year-old men with untreated mild essential hypertension (●; n = 12; BP: 154 ± 3/100 ± 3 mmHg; means ± SE) and normotensive control men given adrenaline (○; n = 11; BP 124 ± 3/78 ± 2 mmHg) and sodium chloride 0.9% (△; n = 12; BP: 126 ± 3/80 ± 1 mmHg). Adrenaline infusion was increased by 0.01 μg/kg/min every 10 min giving arterial concentrations of 4–500 pg/ml after 40 min. *p < 0.05; **p < 0.01; ***p < 0.001. Data from Lande et al. (6).

lation between HDL and triglycerides was expected (9). Catecholamines seem to inactivate lipoprotein lipase (10), possibly through effects mediated by alpha-adrenoceptors (11). Such a mechanism may explain the positive correlation between LDL + VLDL cholesterol and increased arterial adrenaline in subjects with essential hypertension (5) and also, in animals, the increased total cholesterol level due to elevation of plasma adrenaline within the pathophysiological range (12).

Both $beta_1$-selective and the combined $beta_1$- and $beta_2$-adrenoceptor blockade lower HDL and increase triglyceride concentrations (9, 11, 13). The mechanisms by which beta-adrenoceptor blockade induces these metabolic effects are uncertain. However, both $beta_1$-selective and combined $beta_1$- and $beta_2$-adrenoceptor blockade increase circulating adrenaline, especially during exercise (Gullestad et al., to be published). It has been suggested (11) that elevated plasma catecholamines during long-term beta-adrenoceptor blockade exert their inhibiting effect on lipoprotein lipase through unopposed alpha-adrenoceptor activity (Fig. 3), in harmony with the general tendency of alpha-adrenoceptor blockade to oppose the effects of beta-adrenoceptor blockade on blood lipoproteins (13).

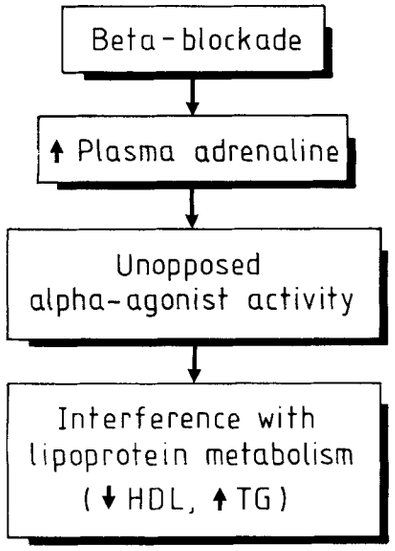

Fig. 3. Mechanisms by which plasma adrenaline may interfere with lipoprotein metabolism. HDL: high-density lipoprotein; TG: triglyceride. Initially suggested by Day et al. (9).

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References

1. Kjeldsen SE, Flaaten B, Eide I, Helgeland A, Leren P: Evidence of increased peripheral catecholamine release in patients with long-standing, untreated essential hypertension. *Scand J Clin Lab Invest* **42**: 217–223 (1982).
2. Kjeldsen SE, Eide I, Aakesson I, Leren P: Increased arterial catecholamine concentrations in 50-year-old men with essential hypertension. *Scand J Clin Lab Invest* **43**: 343–349 (1983).
3. Mörlin C, Wallin BG, Eriksson BM: Muscle sympathetic activity and plasma noradrenaline in normotensive and hypertensive man. *Acta Physiol Scand* **119**: 117–121 (1983).

4. Julius S, Pascual AV, London R: Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation* **44**: 413–418 (1971).
5. Kjeldsen SE, Gjesdal K, Eide I, Aakesson I, Amundsen R, Foss OP, Leren P: Increased β-thromboglobulin in essential hypertension: interactions between arterial plasma adrenaline, platelet function and blood lipids. *Acta Med Scand* **213**: 369–373 (1983).
6. Lande K, Kjeldsen SE, Os I, Westheim A, Hjermann I, Eide I, Gjesdal K: Increased platelet and vascular smooth muscle reactivity to low-dose adrenaline infusion in mild essential hypertension. *J Hypertens,* **6**: 219–225 (1988).
7. Hollister AS, Onrot J, Lonce S, Nadeau JHJ, Robertson D. Plasma catecholamine modulation of alpha-2 adrenoceptor agonist affinity and sensitivity in normotensive and hypertensive human platelets. *J Clin Invest* **77**: 1416–1421 (1986).
8. Patsch JR, Gotto AM, Olivecrona T, Eisenberg S: Formation of high density lipoprotein$_2$-like particles during lipolysis of very low density lipoprotein in vitro. *Proc Natl Acad Sci* **75**: 4519–4523 (1978).
9. Kjeldsen SE, Eide I, Leren P, Foss OP, Holme I, Eriksen IL: The effect of HDL cholesterol of oxprenolol and atenolol. *Scand J Clin Lab Invest* **42**: 449–453 (1982).
10. Ashby P, Parkin S, Walker K, Bennett DP, Robinson DS: Hormonal control of adipose tissue lipoprotein lipase activity. *INSERM Symposia* **87**: 149–159 (1979).
11. Day JL, Metcalfe J, Simpson CN: Adrenergic mechanisms in control of plasma lipid concentrations. *Br Med J* **284**: 1145–1148 (1982).
12. Dimsdale JE, Herd A, Hartley H: Epinephrine mediated increases in plasma cholesterol. *Psychosomatic Med* **45**: 227–232 (1983).
13. Leren P, Foss OP, Helgeland A, Hjermann I, Holme I, Lund-Larsen PG: Effect of propranolol and prazosin on blood lipids. The Oslo Study. *Lancet* **ii**: 4–6 (1980).