Response of Plasma Lipids and Platelet Aggregation to Intravenous Arginine[1] (37472)

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(Introduced by S. Rosenfeld)

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Previous work from this laboratory showed glucagon lowered plasma lipids in human subjects by transfer of the lipid to blood platelets with accompanying inhibition of epinephrine-induced platelet aggregation (1, 2). Evidence in support of this conclusion was: (a) whole blood total lipid was not depressed even though plasma lipid was significantly lowered; (b) incubation of aliquots of whole blood following glucagon administration completely or partially restored depressed plasma lipid levels; and (c) *in vitro* study showed glucagon lowered plasma lipids in platelet-rich plasma (PRP) only while there was no change in platelet-poor blood or "cell-free" plasma. The question arose as to whether pancreatic glucagon secreted into the portal vein and carried directly to the liver would have the same effect on plasma lipids and platelet aggregation as exogenous glucagon. Since intravenous arginine stimulates glucagon secretion (3), this study was done to determine the effect of arginine on plasma lipids and platelet aggregation.

Materials and Methods. Venous blood was taken from 17 normal volunteers recruited from hospital personnel using plastic syringes and sodium citrate (19%, 0.18 ml/10 ml blood). There were 7 men (ages 23–45) and 10 women, 9 of whom were premenopausal (ages 21–33) while the tenth was 4 years postmenopausal (age 53). All subjects were in good health and had not taken aspirin or other medication for at least 2 weeks prior to study. None of the women had ever taken oral contraceptives. Four hundred milliliters of 5% arginine hydrochloride (R-Gene, Cutter Laboratories) in distilled water were given intravenously over a 30 min period. Subjects continued their daily routines, and blood was taken at 1, 2, and 3 hr. At a later date, 4 subjects (2 men and 2 women) were given 400 ml 0.45% saline as a control study. All glassware was siliconed. An aliquot of whole blood was removed for determination of whole blood total lipid. The remaining blood was centrifuged 10 min at 115–135*g* in a swinging bucket head at room temperature to obtain PRP. PRP was removed, and the remaining specimen spun at 850*g* to obtain platelet-poor plasma (PPP). Temperature of the spun material did not exceed 26°. Platelet aggregation was induced in 1.0 ml PRP by epinephrine (Adrenalin Chloride, Parke-Davis) in final concentration of 5×10^{-6} *M*, and absorbance measured in arbitrary units using a platelet Aggregometer (Chrono-Log Corp., Broomall, Pa.) as previously described (2). All plasma lipid determinations were done on PPP. Plasma and whole blood total lipid (4); triglycerides (5); cholesterol (6); phospholipid (7), and free fatty acids (FFA) (8) were done in duplicate.

Results. Figures 1, 2, 3, and 4 show the effect of 400 ml intravenous arginine in distilled water on plasma and whole blood total lipid; cholesterol and phospholipid; triglyceride and FFA, and epinephrine-induced secondary platelet aggregation, respectively, of a group of 7 men and another group of 10 women. The effect of 400 ml 0.45% saline is also shown. The data were calculated as percent increase or decrease from 0-hr values for each individual. Each point on the graphs

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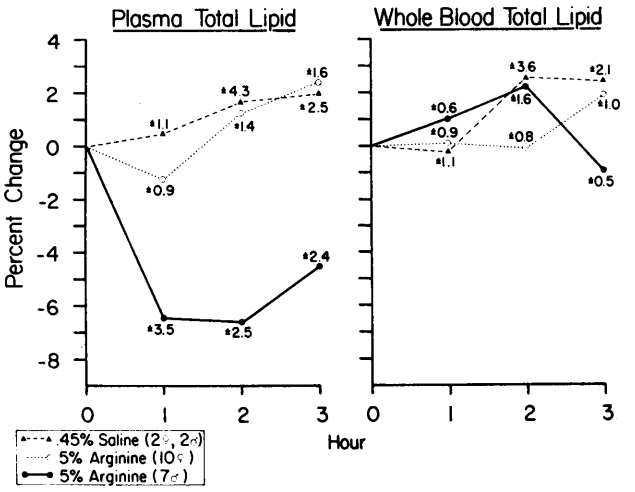

FIG. 1. Effect of 400 ml intravenous 5% arginine and 0.45% saline on plasma and whole blood total lipid of normal men and women.

is the Mean ± SE for the groups. Mean 0-hr lipid levels and ranges for each group are shown in Table I. Epinephrine-induced secondary platelet aggregation was expressed as absorbance (arbitrary units), and each point on the graph is the Mean ± SE for each group. Secondary platelet aggregation was induced in 0-hr PRP by epinephrine in 5 of 7 men (72%), 7 of 10 women (70%) and in all 4 individuals in the saline control group.

Intravenous arginine caused depression of all plasma lipid fractions and inhibition of epinephrine-induced platelet aggregation in men only. Comparison of plasma lipid depressions in men with saline control values by the Student's t test showed the following: total lipid, $p < 0.05$ at 3 hr; cholesterol, $p < 0.02$ at 2 and 3 hr; phospholipid, $p < 0.05$ at 1 and 3 hr; triglycerides, $p < 0.02$ at 1 and 2 hr, and FFA, $p < 0.01$ at 1 hr. Inhibition of secondary platelet aggregation was significant at 3 hr ($p < 0.05$). There was no depression of plasma lipid fractions except

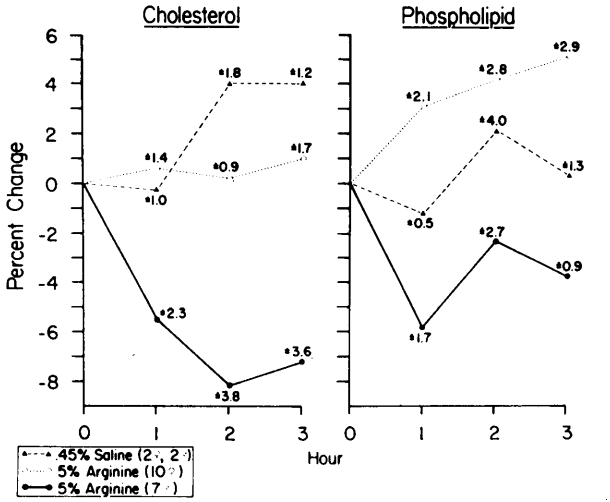

FIG. 2. Effect of 400 ml intravenous 5% arginine and 0.45% saline on plasma cholesterol and phospholipid of normal men and women.

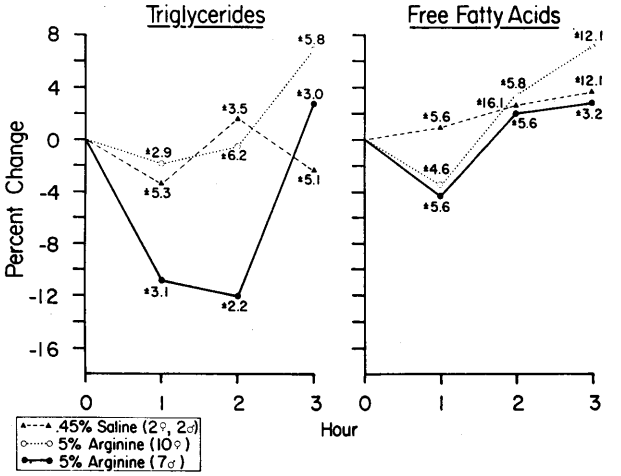

FIG. 3. Effect of 400 ml intravenous 5% arginine and 0.45% saline on plasma triglycerides and free fatty acids of normal men and women.

FFA ($p < 0.02$ at 1 hr) nor inhibition of platelet aggregation in the female group. 0.45% saline had no effect on plasma lipids or platelet aggregation. 0.45% saline was chosen as the control diluent as it was thought normal saline would cause too great an expansion of plasma volume while 5% dextrose would introduce new and complicating factors such as suppression of glucagon secretion (3).

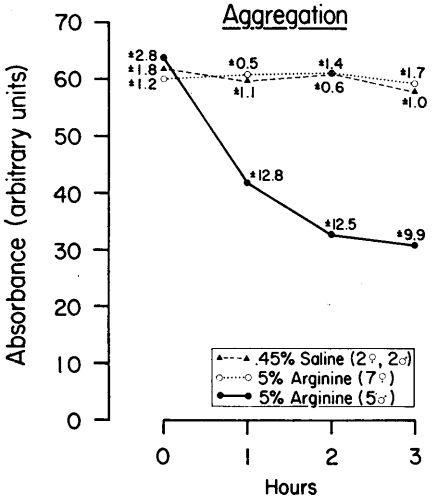

FIG. 4. Effect of 400 ml intravenous 5% arginine and 0.45% saline on secondary platelet aggregation induced by 5×10^{-6} *M* epinephrine in normal men and women.

Discussion. This study showed intravenous arginine caused depression of plasma lipids and inhibition of epinephrine-induced platelet aggregation in men only. The similarity of response to arginine in men with that following glucagon administration indicates depression of plasma lipids with accompanying inhibition of epinephrine-induced platelet aggregation was probably due to stimulation of pancreatic glucagon secretion. However, no explanation can be given for the lack of response to arginine in women. This was unexpected since exogenous glucagon caused the same magnitude of plasma lipid depression and inhibition of epinephrine-induced platelet aggregation in men and women (1, 2). We are not aware of any reports showing arginine causes differences in response of pancreatic glucagon secretion in men and women. Intravenous arginine also stimulates growth hormone (GH) secretion, and Merimee *et al.* reported arginine may sometimes cause greater secretion of GH in women than men (9). It is possible greater GH secretion may have occurred in women in the present study and was responsible for absence of plasma lipid depression and inhibition of epinephrine-induced platelet aggregation by some unknown mechanism.

Intravenous arginine stimulates secretion of insulin as well as GH (9), and the possible

TABLE I. Mean 0-hr Lipid Values.[a]

	Men	Women	Saline
Total lipid	430	518	504
mg (%)	(376–474)	(406–832)	(434–595)
Cholesterol	210	254	216
mg (%)	(163–270)	(176–450)	(182–240)
Phospholipid	188	212	210
mg (%)	(162–206)	(150–309)	(169–257)
Triglycerides	60	67	54
mg (%)	(33–104)	(26–208)	(45– 65)
FFA	496	531	683
μEquiv/liter	(394–563)	(187–746)	(515–750)
Whole blood			
Total lipid	402	474	503
mg (%)	(348–447)	(372–663)	(487–540)

[a] Parentheses indicate range.

role of these hormones in lowering plasma lipids and inhibiting epinephrine-induced platelet aggregation in men should be considered. Insulin lowers plasma lipids only when lipids are elevated due to impaired carbohydrate metabolism as in diabetic ketosis. Insulin does not lower plasma lipids (other than FFA) in normal people (10, 11) nor depress plasma cholesterol in normal dogs (12). Jones and Arky reported insulin lowered plasma triglycerides in normal people; however, insulin was given as constant infusion for 5–8 hr with some depression of plasma triglycerides beginning at 3 hr (13). In the present study, plasma triglycerides were significantly depressed at 1 and 2 hr in the male group and had returned to normal levels by 3 hr. We are not aware of any reports that GH lowers plasma lipids other than FFA which are depressed at 1 hr and subsequently elevated (14). If GH were responsible for depression of plasma lipids and inhibition of platelet aggregation, then women should have also responded like men.

Plasma FFA were depressed at 1 hr with subsequent elevation in both men and women following arginine. This is the same pattern of plasma FFA response caused by either glucagon (15), insulin or GH (14) all of which depress FFA during the first hour by promoting glucose utilization. The depression of plasma FFA in both men and women was probably due to the combined effects of glucagon, insulin and GH secretion.

Intravenous arginine had the same effect in men as exogenous glucagon on plasma lipids and platelet aggregation. It appears stimulation of pancreatic glucagon secretion by intravenous arginine was responsible. No explanation can be given why men responded to arginine with depression of plasma lipids and inhibition of platelet aggregation while women did not.

Summary. Intravenous administration of 400 ml 5% arginine in distilled water to 7 men and 10 women caused depression of plasma lipids and inhibition of epinephrine-induced platelet aggregation in men only. There was no depression of plasma lipids (except FFA) nor inhibition of platelet aggregation in women. 0.45% saline had no effect on plasma lipids or platelet aggregation. The similarity of response of plasma lipids and platelet aggregation in men following arginine with that after glucagon administration indicates the findings in men were probably due to stimulation of pancreatic glucagon secretion by arginine. No explanation can be given for the lack of response in women.

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