Chapter 5

Discussion.

The effects of intravenous ARG infusion before and after IND administration would be divided into 3 parts :

1) effects on water clearance and electrolyte excretion
2) effects on renal hemodynamics
3) effects on systemic hemodynamics

1) Water clearance and electrolyte excretion

The ARG infusions before and after IND administration increased urine flow, Cosm in both groups of dogs. These effects were markedly observed during the infusion period and gradually disappeared when the infusion stopped. These were the results of the osmotic diuresis most likely from ARG. The osmotic diuresis also caused acute rises in FENaand FEK. During the period of IND administration, urine flow, FENa and FEK tended to decrease whereas C_{H_2O} was impaired although the values did not reach statistical significance, comparing with the period just before IND administration. These effects occurred from the inhibition of prostaglandin synthesis by non-steroidal antiinflammatory drugs such as IND. Prostaglandin cyclooxygenase inhibitors enhanced ADH

stimulation of water reabsorption (Anderson et al., 1975 ; Berl et al., 1977 ; Leyssac et al., 1975 ; Lum et al., 1977), antagonized natriuretic effect of prostaglandins and induced hyporeninemic hypoaldosteronism (Hart and Lifschitz, 1987). A decrease in FEK would be the results of reduced urine flow and/or the effect of hypoaldosteronism.

2) Renal hemodynamics

In this study under the normal condition ARG infusion in both groups only slightly reduced RVR without significant rises in GFR and RPF. These results suggested the weak renal vasodilatation effect of ARG in the presence of prostaglandins, at the normal condition. IND administration reduced RPF significantly whereas GFR did not change significantly, resulting in an increase in FF. The result agrees with that of the previous reports (Feigen et al., 1976 ; Herbaczynska-Cedro and Vane, 1973 ; Lonigro et al., 1973 ; Terragno et al., 1977 ; Venuto et al., 1975). In acutely stress animal such as anesthetized, laparotomized dogs, IND reduces RPF without affecting GFR. Prostaglandins thus plays an important role in maintenance renal perfusion during stress. When prostaglandins synthesisis blocked the predominant actions of vasoconstritive hormones lead to reduction in RPF without alteration in GFR.

Interstingly, the second ARG infusion caused a rise

in GFR and RPF, comparing with the IND-treated period in both groups. GFR and RPF were increased in the nearly equal proportion.GFR and RPF were increased by 40% and 47% respectively in group 1 dogs whereas they were increased by approximately twofolds in group 2 dogs. The increase in GFR and RPF were dose dependent, being more marked in group 2 (Figure B). RVR was significantly reduced in group 2 dogs (Figure C). These results thus indicated that the renal vasodilatation was not prostaglandin-mediated and the response was dose dependent. FENa was increased during ARG infusion which could have decreased the GFR if tubuloglomerular feedback were operating. Therefore, tubuloglomerular feedback was unlikely to be the mechanisms of the ARG induced rise in GFR and RPF.

It is possible that ARG infusion stimulates the release of other vasodilators. Growth hormone and glucagon are among the possibilities. ARG is known to stimulate the release of growth hormone (Daughaday, 1985) and glucagon (Rocha et al., 1972). Growth hormone could induce the rise in GFR and RPF in long term administration (Christiansen et al., 1981). However, Hirschberg demonstrated that growth hormone played no role on renal hemodynamic changes induced by amino acid loading (Hirchberg and Kopple, 1988). Glucagon infusion induced renal vasodilatation causing the rise in GFR and RPF (Johannesen, Lee and Kiil, 1977; Parvinget al., 1980)

and affected systemic hemodynamics too. Although there are no data on growth hormone and glucagon in this study the results are of interest. The findings are interpreted to indicate that these vasodilators, whatever they may be, are inactive or play a minor role in renal hemodynamics under the normal condition, but become active when the body needs.

3) Systemic hemodynamics

IND administration increased TPR through vasoconstriction from prostaglandin-synthetic blockade. MAP was slightly increased. An increase in vascular resistance thus reduces the venous return to heart, resulting in depression of CO (Braunwald andRoss, 1973). In some report the change in CO may not be significant (Lonigro et al., 1973).

The first ARG infusion at higher dose decreased TPR and increased CO whereas lower dose did not. These findings suggested that ARG infusion induced systemic vasodilatation and increased CO in a dose dependent manner. The second ARG infusion had no significant effect on TPR and MAP but increased CO when compared with the IND-treated period. The unchanged TPR during the second ARG infusion indicates that systemic vasodilatation caused by ARG could not overcome the vasoconstriction caused by IND. The significant increase in CO by ARG without significant changes of TPR and HR

following IND administration suggests the direct effect of ARG on the contractility of the heart. This effect was strong enough to overcome the CO reducing effect of IND. It is possible that the hemodynamic effect of ARG is mediated through glucagon which enhances cardiac contractility and reduces peripheral resistance (Parmley, Glick and Sonneblick, 1968). Unfortunately the glucagon level was not measured.

Relationship between Renal and Systemic hemodynamics

The increase in GFR and RPF due to the renal vasodilatation during the second ARG infusion in group 1 dogs occurred in spite of insignificant change of CO (Figure D). Moreover, significant increase in CO during the first ARG infusion in group 2 dogs occurred without significant renal vasodilatation (Figure E). These results indicated that ARG had the effects on both systemic and renal hemodynamics but renal hemodynamic changes were independent upon the systemic hemodynamic changes.

Summary

This experiment demonstrates that an acute ARG loading induces renal and systemic vasodilatation in a dose dependent manner despite IND effect and would indicate that renal hemodynamic changes are not prostaglandin-mediated. The renal hemodynamic changes are indepcndent upon the systemic hemodynamic changes.