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Beneficial Effects of Maximal Hydration on Early Renal Function After Ischemia Is Mediated by Atrial Natriuretic Factor

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ATRIAL natriuretic factor (ANF), a physiological substance released from the atria of mammals, including humans, appears not only as a powerful natriuretic substance, but also as a modulator of glomerular filtration rate (GFR), renal blood flow, and renal vascular resistance.¹ Moreover, maximal loading appears to be an important physiological stimulus for ANF release.² This study was designed to assess whether ANF improves the early renal function after ischemia in dogs, and to define whether the beneficial effect of maximal volume loading is mediated by ANF.

MATERIAL AND METHODS

Twenty-eight mongrel dogs (18 to 23 kg) of both sexes were anaesthetized with pentobarbital sodium (30 mg/kg/IV), intubated, and ventilated. A femoral artery catheter was used for systolic BP measurement, cardiac rhythm monitoring, and blood samples.

A tipped balloon Swan-Ganz catheter (SI, American Edwards Lab, Puerto Rico) was advanced through the internal jugular vein into the pulmonary artery for measurement of pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP). Right atrial pressure (RAP) was measured using a certofix catheter (Braun, FRG) introduced in the right atria through the left jugular vein.

The right femoral vein was cannulated for administration of tritiated labelled inulin dissolved in NaCl 0.9% (Amersham, England) at a rate of 1 mL/min; by continuous infusion before the experiment, an equilibrium state is reached within two hours. Through a small midline laparotomy, both ureters were thereafter cannulated for measurement of urinary output and 3H inulin clearance (GFR).

Two hours later, the dogs underwent a right nephrectomy and a left kidney skeletization to eliminate the capsular arterial blood supply and the renal innervation. After this surgical approach, the left renal artery was occluded with a vascular clamps for 45 minutes. The early renal function recovery was assessed every 30 minutes after declamping for two hours analyzing the following

parameters: GFR; urinary output, sodium, potassium or chlorides excretion rate; serum creatinine, urea, sodium, potassium, chlorides, hematocrit. Systolic PAP, PCWP, RAP were measured in the same times.

Three experimental groups were achieved:

1. *Group 1* ($n = 10$) (control group) Each dog received during the whole experiment isotonic saline solution (NaCl 0.9%) at a rate of 0.2 mL/min/kg.

2. *Group 2* ($n = 10$): All animals received an acute infusion of whole blood at a rate of 1 mL/kg/min during the 45 minutes of warm ischemia and after declamping received only isotonic saline at the same rate than in the controls.

3. *Group 3* ($n = 8$) (ANF group) After ischemia, all dogs received ANF infusion at low dose (3.6 pg/kg/min) for the two hours of renal recovery. 1-28 human ANP (Peninsula Laboratories, England) dissolved with 1 mL of 0.1% acetic acid and 4 mL of human albumin was infused in isotonic saline solution at the same rate as in the controls (0.2 mL/kg/min).

ANF plasma levels (pg/mL) were measured in arterial blood withdrawn through the femoral artery catheter every 30 minutes after declamping. Plasma ANF levels were obtained by radioimmunoassay using rabbit antibodies against 1-28 human ANP (Peninsula Laboratories, England). The comparison between the three experimental groups and multiple comparisons two by two were achieved using a nonparametric analysis of variance; the Kruskal-Wallis test.

RESULTS

At 0 and 30 minutes after declamping, the PAP, PCWP, and RAP were significantly

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higher in group 2 (hyperhydrated animals) than in the control and ANF groups (Fig 1).

Moreover, these increased pressures were correlated with an endogenous ANF release since ANF plasma levels reached at 0 minute 357.5 ± 92 pg/mL in group 2 v 60 ± 4.1 in control group and 118.5 ± 26 pg/mL in ANF group ($P < .01$ and $P = NS$, respectively). At 30 minutes, ANF plasma levels in group 2 remain higher than in the controls (240.6 ± 56 pg/mL v 67.7 ± 5 , $P < .01$), whereas the difference with ANF group is not statistically

significant. ANF levels were, after 30 minutes, similar in group 2 and 1, whereas in ANF group, the plasma ANF levels remain higher than in control group for the whole two hours of renal function recovery (Fig 2).

Regarding the renal function parameters tested, this study clearly demonstrated that hyperhydration or ANF infusion improves the early renal function recovery in terms of urinary flow, sodium excretion rate, and GFR when compared with the controls. The beneficial effects of maximal loading is nevertheless

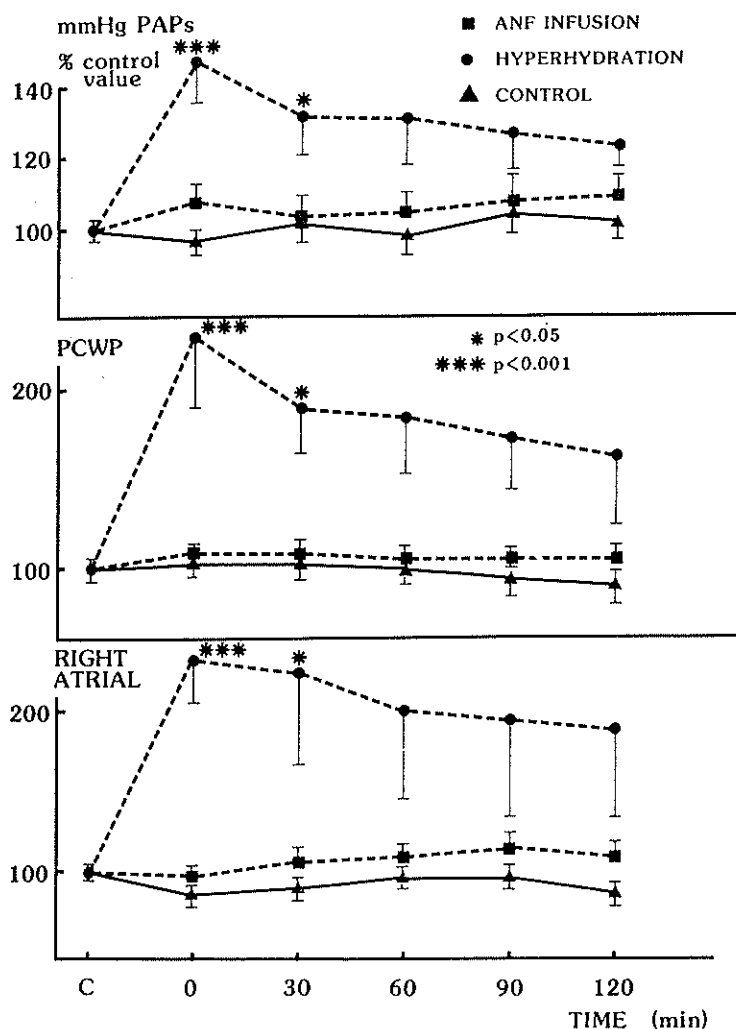
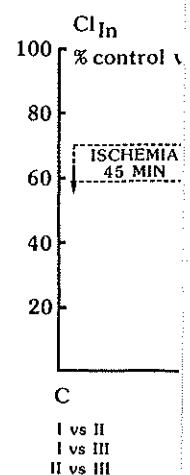


Fig 1. Pulmonary, capillary, and right atrial pressures evolution during the whole experiment.

Fig 2. ANF p variation in each g

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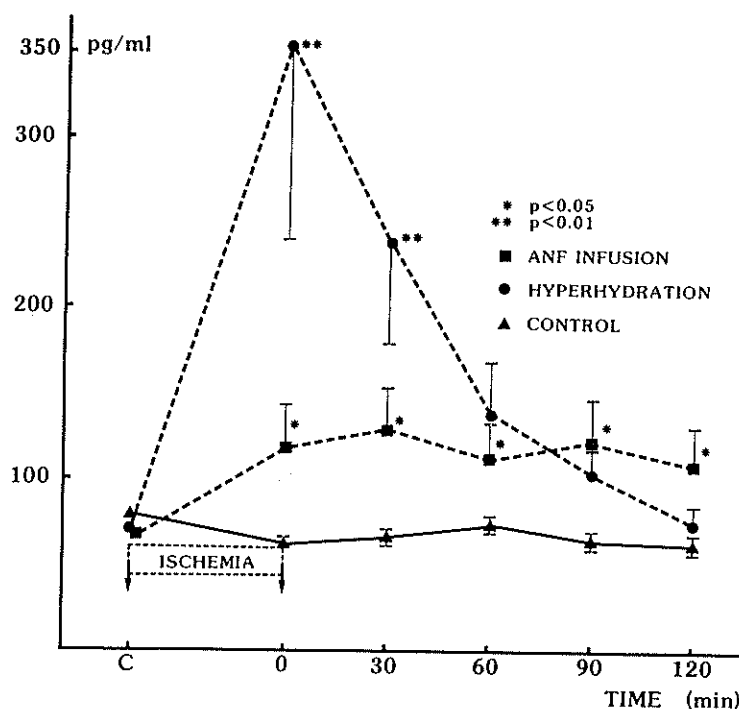


Fig 2. ANF plasma levels variation in each group.

transient since at two hours the GFR recovery was similar in groups 1 and 2 with similar PAP, PCWP, RAP pressures, and ANF plasma levels at this time.

The GFR recovery after warm ischemia was improved by maximal loading at 60 and

90 minutes after declamping in group 2 and every time by human 1-28 ANF infusion after ischemia (Fig 3).

Similar results were obtained upon urinary flow which, two hours after declamping, was ten times higher in group 2 and 15 times

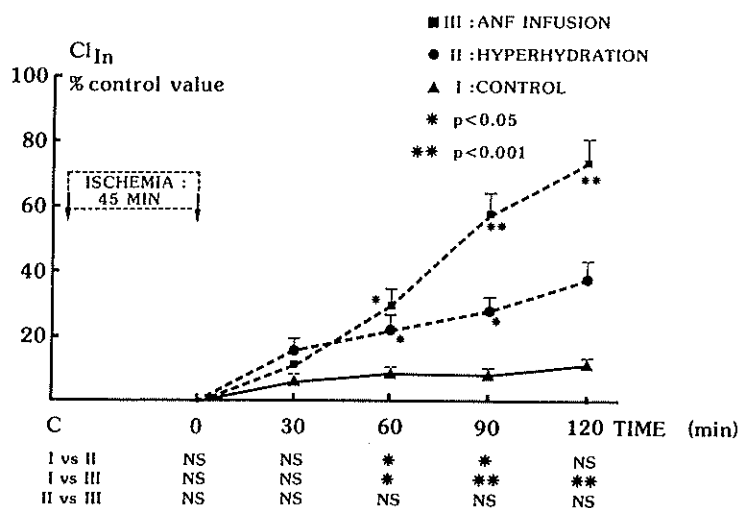


Fig 3. Glomerular filtration rate recovery after acute renal (45 min) ischemia.

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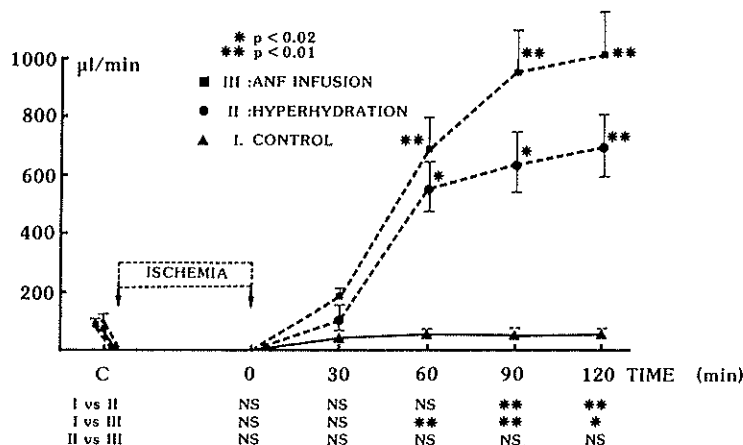


Fig 4. Urinary flow after acute renal ischemia.

higher in group 3 as compared with the controls (Fig 4). The urinary sodium excretion rate follows the same enhancement and was two hours after the end of ischemia, 15 times higher in group 2 and 20 times higher in group 3 than in the controls (Fig 5).

DISCUSSION

This study clearly demonstrated that ANF release occurs after maximal loading resulting

from atrial distension. Hyperhydration leads therefore to better renal function recovery after renal ischemia in terms of GFR, urinary flow, and sodium excretion rate, but these beneficial effects were transient. By contrast, human ANF infusion at low doses after ischemia leads comparable but more durable results on the early renal function recovery. Thus, this study suggest that ANF is an important modulator of intrarenal hemodynamics and the hormonal mediator of hyper-

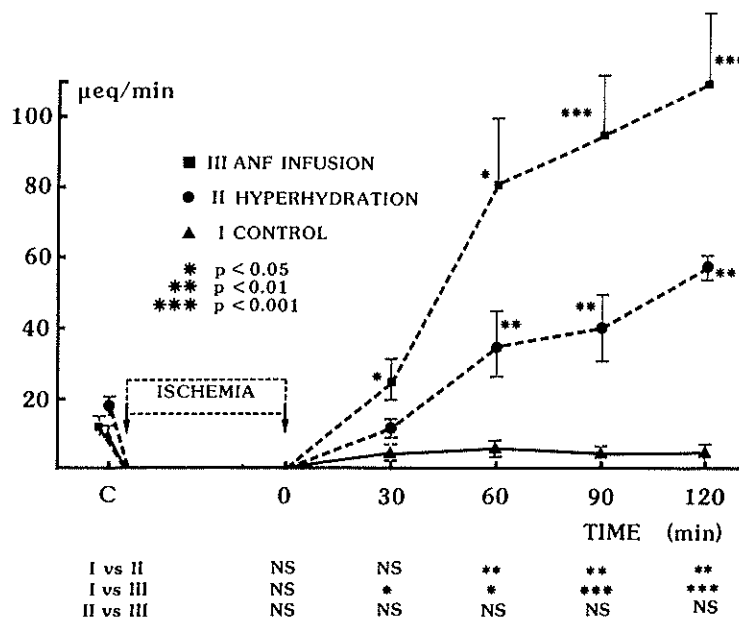


Fig 5. Urinary sodium excretion rate in each group, during the whole experiment.

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