Q J Med 1998; **91**:367–369

Ammonia concentration in the renal veins in unilateral renal artery stenosis with hypertension

B. AGROYANNIS, D. MOURIKIS, I. KOPELIAS, H. TZANATOS, L. SOUBASSI and C. FOURTOUNAS

From the Department of Nephrology, Aretaieon University Hospital, Athens, Greece.

Received 3 November 1997 and in revised form 16 February 1998

Summary

We measured blood ammonia in pre-angioplasty samples from the renal veins, aorta and inferior vena cava of 15 patients with hypertension due to unilateral renal artery stenosis confirmed by arteriography. Patients with renal insufficiency or small kidneys were excluded. Mean ammonia values were μg/dl: vein of affected kidney, 106.00 ± 12.75; vein of unaffected kidney, 75.65 ± 23.10; aorta 61.04 ± 15.00; vena cava, 62.44 ± 19.65. The value for the affected kidney was significantly higher than the other three values ($p < 0.001$). Mean ± SD DTPA uptake (%) was 42.8 ± 2.21 in the affected kidney and 56.53 ± 3.64 in the unaffected kidney. This difference did not correlate significantly with that of the ammonia concentrations $\tau = -0.292$).

Introduction

An important function of the kidney is the production of ammonia, which is formed mainly in the proximal tubule. The primary substrate for renal ammonia production is glutamine. Factors which influence renal ammonia production include angiotensin II, potassium and aldosterone.[1–4] There is strong evidence that an important intrarenal renin-angiotensin system exists, which produces angiotensin II; this production exerts important effects on the function of the proximal tubule. In unilateral renal artery stenosis, angiotensin I production in the affected kidney is seven times higher than in the contralateral kidney, and the majority of angiotensin II in renal venous blood of the kidney with renal artery stenosis is attributed to intrarenal production.[5–8]

We determined the ammonia concentration in blood collected from the renal veins, aorta and inferior vena cava of patients with unilateral renal artery stenosis and hypertension.

Methods

We studied 15 patients, aged 27–68 years (median 51 years) with hypertension due to unilateral renal artery stenosis. None showed dysfunction of any major organ, and their diastolic blood pressures, without medication, were >110 mmHg. Patients had normal renal function (CrCl >95 ml/min) and the size of the two kidneys was within normal limits. The relative DTPA uptake of the affected kidney was 38–45%. Patients with renal insufficiency and small kidneys were excluded from the study. In all patients the diagnosis of renal artery stenosis was established by angiography.

The present study includes only patients whose hypertension was improved or cured by angioplasty of the affected renal artery at follow-up of at least 6 months. This enhances the evidence that their hypertension was caused by the stenosis. Subjects discontinued the antihypertensive treatment for 24 h, and were admitted to hospital for angioplasty of the affected renal artery. Before the angioplasty procedure, blood samples were collected from the aorta, from both renal veins and from the inferior vena cava.

Ammonia was determined by a colorometric method (Wako Chemicals GmbH). Normal values ranged from 30 to 86 μg/dl). Statistical analysis used Student's t test and linear regression.

Address correspondence to Associate Professor B. Agroyannis, Department of Nephrology, Aretaieon University Hospital, 76 Vas. Sofias Avenue, GR–115 28 Athens, Greece

© Oxford University Press 1998

Results

Our data show a difference of blood ammonia concentration between the renal veins in patients with hypertension and unilateral renal artery stenosis (Figure 1). Mean values ($\pm$SD) of blood ammonia (μg/dl) were: vein of affected kidney, 106.00$\pm$12.75; vein of unaffected kidney, 75.65$\pm$23.10; aorta, 61.04$\pm$15.00; and inferior vena cava, 62.44$\pm$19.65. The ammonia concentration in the vein of affected kidney exceeded the normal limits, and was significantly higher than that in the renal vein of the unaffected kidney, that of the aorta or that of the inferior vena cava ($p<0.001$).

The mean DTPA uptake (%) in the affected kidney was 42.8$\pm$2.21; that in the unaffected kidney was 56.33$\pm$3.64. The difference in ammonia between the two renal veins was not significantly correlated with the difference in DTPA uptake between the kidneys (Figure 2).

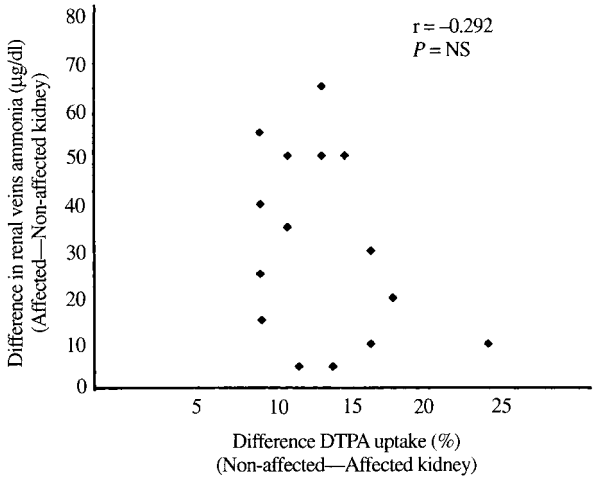

Figure 2. Difference in DTPA uptake (%) between affected and unaffected kidneys is not correlated with the difference in ammonia in their renal veins.

Discussion

Our results show that ammonia production differs between the two kidneys in patients with unilateral renal artery stenosis and hypertension. Ammonia is produced by the kidney at a high rate in the proximal tubule, which is a target for the action of angiotensin II. The major substrate for the synthesis of ammonia in the kidney is glutamine. In normal subjects, the difference between renal venous and arterial ammonia is moderately positive. This indicates that ammonia produced in the kidney is released into the renal veins and consequently into the systemic circulation.[2,3,9,10] Factors which influence the production of ammonia in the kidney include angiotensin II, potassium and aldosterone.[2,3,4,10] Recent studies have suggested that angiotensin II concentration is higher in intrarenal fluid compartments than in the systemic circulation, and there is evidence that an intrarenal renin-angiotensin II system generates angiotensin II. This local production of angiotensin II increases in renal ischaemia and hypertension. In patients with unilateral renal artery stenosis and hypertension, the production of renin is increased in the affected kidney, but decreased in the unaffected kidney, and angiotensin II in the renal vein of the affected kidney is higher than in that of the unaffected kidney. This suggests that the majority of angiotensin II in the venous blood of the kidney with arterial stenosis is generated intrarenally. The renal extraction of angiotensin II is significantly higher in the unaffected than in the affected kidney. This indicates that the excessive angiotensin II produced in the affected kidney is eliminated by the unaffected kidney.[5–8,11]

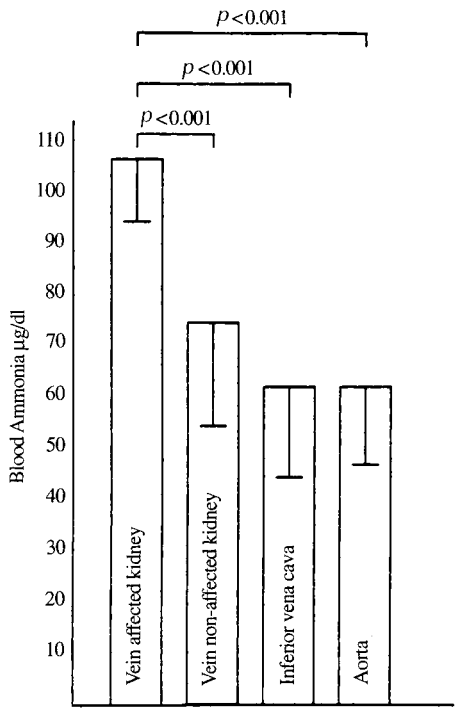

Figure 1. Blood ammonia concentrations in the renal vein of affected and unaffected kidneys, in the aorta and in the inferior vena cava, in patients with unilateral renal artery stenosis and hypertension.

Angiotensin II influences the functioning of the proximal tubule, including the production and transport of ammonia. Angiotensin II has a concentration-dependent effect on NH_3 production and secretion: at concentrations of about 10^{-10}–10^{-8} M, it stimulates NH_3 production but inhibits luminal secretion. Saralasin (an angiotensin II antagonist) inhibits the stimulatory effect of angiotensin II on NH_3 production in the proximal tubule. The action of angiotensin II in enhancing ammonia production in the proximal

tubule provides strong evidence that angiotensin II may be an important regulator of acid-base balance.[2,3,9]

Other factors which may influence the production of ammonia in the kidney include changes in serum potassium and aldosterone. In potassium depletion, the intrarenal production of ammonia is increased, whereas with high potassium it is decreased. Administration of aldosterone may increase renal ammonia production, independently of alterations in potassium balance. However, the administration of mineralocorticoids, in experimental animals, may cause increased excretion of ammonia and potassium depletion. Angiotensin II is thought to cause vasoconstriction and augmentation of aldosterone secretion. This moderate hyperaldosteronism in renovascular hypertension may thus contribute to the increase in renal ammonia production.[4,8] The discrepancy we have found in ammonia concentration between the renal veins supports the concept that the intrarenal production of components of the renin-angiotensin system, mainly angiotensin II, influences renal ammonia production. The observation that this discrepancy is not correlated with difference in DTPA uptake is indirect evidence that it is not due to the small reduction in glomerular filtration rate. On the other hand, reduction in renal mass is accompanied by an adaptive increase in ammonia production in the remaining nephrons, producing a higher than expected urinary ammonium excretion rate, and this could have some bearing on our results.[12]

Our results suggest that determination of renal vein ammonia may have diagnostic value in patients with renovascular hypertension. However, more research is needed before measurement of ammonia in renal venous blood can be used to make clinical decisions about patient care.

References

1. Liu FY, Cogan MG. Angiotensin II: A potent regulator of acidification in the rat early proximal convoluted tubule. *J Clin Invest* 1987; **80**:272–5.
2. Chobanian MC, Julin CM. Angiotensin II stimulates ammoniagenesis in canine renal proximal tubule segments. *Am J Physiol* 1991; **260**:F19–26.
3. Nagami GT. Effect of Angiotensin II on ammonia production and secretion by mouse proximal tubules perfused *in vitro*. *J Clin Invest* 1992; **89**:925–31.
4. Tannen RL, Sahai A. Biochemical pathways and modulators of renal ammoniagenesis. *Miner Electrolyte Metab* 1990; **6**:249–58.
5. Seikaly MG, Aranr BS, Seney DF. Endogenous Angiotensin concentrations in specific intrarenal fluid compartnments of the rat. *J Clin Invest* 1990; **86**:1352–7.
6. Burns KD, Homma T, Harris RC. The intrarenal renin-angiotensin system. *Semin Nephrol* 1993; **13**:13–30.
7. Pedersen EB, Eiskjaer H, Madsen B, Danielsen H, Egeblad M, Nielsen CB. Effect of captopril on renal extraction of renin, angiotensin II, atrial natriuretic peptide and vasopresin and renal vein renin ratio in patients with arterial hypertension and unilateral renal artery disease. *Nephrol Dial Transpl* 1993; **8**:1064–70.
8. Goldfarb DA, Novick AC. The renin-angiotensin system: Revised concepts and implications for renal function. *Urology* 1994; **43**:572–83.
9. Nagami GT. Effect of luminal angiotensin II on ammonia production and secretion by mouse proximal tubules. *Am J Physiol* 1995; **269**:F86–92.
10. Huizenga JR, Gips CH, Tangerman A. The contribution of various organs of ammonia formation: a review of factors determining the arterial ammonia concentration. *Ann Clin Biochem* 1996; **33**:23–30.
11. El Nahas, AM. Renal scarring: the role of angiotensin II. *Nephrol Dial Transplant* 1995; **10(suppl 9)**:28–32.
12. Dass PD, Kurtz I. Renal ammonia and bicarbonate production in chronic renal failure. *Miner Electrolyte Metab* 1990; **16**:308–14.