Kidney International, Vol. 58 (2000), pp. 1356–1357

EDITORIAL

Renal failure: A state of nitric oxide deficiency?

In this issue, Schmidt and Baylis confirm what has been expected by many—though not all—nephrologists, that is, that whole body nitric oxide (NO) production is reduced in renal failure. This observation eliminates any doubt about the direction in which NO production is changed, that is, the composite result of the activities of the NO synthase (NOS) isoforms. As all good scientific communications, however, this observation also raises (and leaves unanswered) a number of issues.

The results of this study should be viewed against the background of past controversies. Using platelets [2] and mononuclear cells stimulated by contact with bioincompatible membranes [3], some investigators postulated that NO production was stimulated in renal failure. In contrast, Vallance and Moncada reported that the plasma concentrations of asymmetric dimethylarginine (ADMA) were elevated in uremic subjects [4]. The NO inhibitory properties of this compound were documented by in vitro (rat aortic ring contraction, inhibition of macrophage NOS activity) and in vivo studies (blood pressure increase in guinea pigs, forearm vasoconstriction in healthy volunteers).

Since the beginning the issue of ADMA concentrations has been plagued by methodological difficulties. Nevertheless, two recent studies provided evidence for increased ADMA plasma concentrations in patients with renal failure [5,6]. However, we do not know whether such ADMA concentrations are inhibitory in vivo [7] and whether the increased concentration is exclusively the result of diminished renal excretion. The latter is somewhat unlikely in view of the observation that the isomer SDMA does not rise strictly in parallel with ADMA. Indeed, altered enzymatic breakdown of ADMA has not been thoroughly excluded [5].

Against this background, what is the main message of the study of Schmidt and Baylis [1]? Both in experimental [8,9] and clinical [10,11] studies it had previously been found that urinary excretion of NOx, that is, the excretion of nitrate and nitrite, an index of the generation of NO, is low in renal failure. However, these studies were not definite, since they did not control for a crucial confounder: dietary intake of NOx. In this respect, the results of the present study are clear cut. They are also in excellent agreement with a recent analysis of arginine-to-citrulline conversion rates in uremic subjects, using $^{15}N_2$-arginine as a substrate for NOS and measuring isotopic plasma enrichment of ^{15}N-citrulline by mass spectrometry (LCMS) [12]. This information obtained with different methodology is in excellent agreement with and complements the observation of Schmidt and Baylis [1]. This point is important, since a priori reduced NOx excretion in the urine might not be the result of reduced synthesis, but of increased elimination of NOx via alternative pathways, for example, interaction with oxygen radicals. In the steady state, reduced renal clearance of NOx should not affect NOx excretion rates, but given the rather high plasma NOx in the study of Schmidt and Baylis one wonders whether NOx clearance is not reduced. There are also observations of diminished acetylcholine-mediated vasodilation in patients with chronic renal failure [13,14], presumably reflecting diminished generation of NO upon stimulation, although the indirect evidence on increased baseline NO production, if confirmed, would potentially point to further complexities.

The statistical power of the study of Schmidt and Baylis is restricted because of the limited sample size and unfortunately the study is incomplete because ADMA, SDMA, and cGMP were not measured in all subjects [1]. The issue of sample size is not trivial, since renal patients may be heterogenous. At least in experimental studies, renal NOS activity was shown to be very much model-dependent (for example, inflammatory vs. noninflammatory) [8,9,15]. Unfortunately, the failure to measure the above parameters in all patients also precludes strong conclusions about factors correlated to NOx excretion and thus provides limited mechanistic insight.

What are the implications of the findings of Schmidt and Baylis [1]? The authors propose the reasonable hypothesis that diminished availability of NOx is important in the genesis of hypertension of renal disease. Even more important may be the role of deficient NOx availability on function and integrity of endothelial cells with implications for atherogenesis, vascular complications, vasomotor tone, etc. It is also not clear whether a similar malfunction of NOS is present in specific compartments, such as the central or peripheral nervous system, with implications for the neuropsychiatric complications of uremia. Finally, there are certain limitations concerning the generalizability of these results. Diminished NOx generation under unstressed conditions does not exclude that

Key words: excretion of NOx, L-arginine, uremia, end-stage renal disease, hypertension, blood pressure.

normal or even excessive amounts of NO are produced under the influence of stimuli such as inflammation, septicemia, bioincompatible treatment modalities, etc.

Can we do something about low NOx production? It would certainly be an attractive thought to administer L-arginine in an effort to overcome reduced NOS activity in order to lower blood pressure and provide endothelial protection. We are afraid, however, that such a straight forward and simplistic approach could be potentially dangerous. For instance, in experimental models of renal disease, depending on the timing of administration of L-arginine and on whether the renal lesion was inflammatory or not, administration was either beneficial or detrimental [16–18]. Thus, the bad news is that we need more information on pathomechanisms involved before we consider interventions based on the observation of Schmidt and Baylis.

Markus Ketteler and Eberhard Ritz
RWTH University Hospital Aachen, and Ruperto-Carola-University Heidelberg, Germany

Correspondence to Prof. Dr. Eberhard Ritz, Department of Internal Medicine, Ruperto-Carola-University Heidelberg, Bergheimer Str. 56a, D-69115 Heidelberg, Germany.
E-mail: prof.e.ritz@t-online.de

REFERENCES

1. Schmidt RJ, Baylis C: Total nitric oxide production is low in patients with chronic renal disease. *Kidney Int* 58:1261–1266, 2000
2. Noris M, Benigni A, Boccardo P, Aiello S, Gaspari F, Todeschini M, Figliuzzi M, Remuzzi G: Enhanced nitric oxide synthesis in uremia: Implications for platelet dysfunction and dialysis hypotension. *Kidney Int* 44:445–450, 1993
3. Amore A, Bonaudo R, Ghigo D, Arese M, Costamagna C, Cirina P, Gianoglio B, Perugini L, Coppo R: Enhanced production of nitric oxide by blood-dialysis membrane interaction. *J Am Soc Nephrol* 6:1278–1283, 1995
4. Vallance P, Leone A, Calver A, Collier J, Moncada S: Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. *Lancet* 339:572–575, 1992
5. MacAllister RJ, Rambausek MH, Vallance P, Williams D, Hoffmann KH, Ritz E: Concentration of dimethyl-L-arginine in the plasma of patients with end-stage renal failure. *Nephrol Dial Transplant* 11:2449–2452, 1996
6. Kielstein JT, Böger RH, Bode-Böger SM, Schaffer J, Barbety M, Koch KM, Frölich JC: Asymmetric dimethylarginine plasma concentrations differ in patients with end-stage renal disease: Relationship to treatment method and atherosclerotic disease. *J Am Soc Nephrol* 10:594–600, 1999
7. Anderstam B, Katzarski K, Bergström J: Serum levels of N^G,N^G-dimethyl-L-arginine, a potential endogenous nitric oxide inhibitor in dialysis patients. *J Am Soc Nephrol* 8:1437–1442, 1997
8. Vaziri ND, Ni Z, Wang XQ, Oveisi F, Zhou XJ: Downregulation of nitric oxide synthase in chronic renal insufficiency: Role of excess PTH. *Am J Physiol* 274:F642–F649, 1998
9. Reyes AA, Karl IE, Yates J, Klahr S: Low plasma and renal tissue levels of L-arginine in rats with obstructive uropathy. *Kidney Int* 45:782–787, 1994
10. Kovacs T, Barta J, Kocsis BB, Nagy J: Nitric oxide in IgA nephropathy patients with or without hypertension. *Exp Nephrol* 3:369–372, 1995
11. Kari JA, Donald AE, Vallance DT, Bruckdorfer KR, Leone A, Mullen MJ, Bunce T, Dorado B, Deanfield JE: Physiology and biochemistry of endothelial function in children with chronic renal failure. *Kidney Int* 52:468–472, 1997
12. Wever R, Boer P, Hijmering M, Stroes E, Verhaar M, Kastelein J, Versluis K, Lagerwerf F, van Rijn H, Koomans H, Rabelink T: Nitric oxide production is reduced in patients with chronic renal failure. *Arterioscler Thromb Vasc Biol* 19:1168–1172, 1999
13. Hand MF, Haynes WG, Webb DJ: Hemodialysis and L-arginine, but not D-arginine, correct renal failure-associated endothelial dysfunction. *Kidney Int* 53:1068–1077, 1998
14. Passauer J, Bussemaker E, Range U, Plug M, Gross P: Evidence in vivo showing increase of baseline NO and decrease of stimulated NO generation in normotensive patients on chronic hemodialysis. *J Am Soc Nephrol* (in press)
15. Ketteler M, Ikegaya N, Brees DK, Border WA, Noble NA: L-arginine metabolism in immune-mediated glomerulonephritis in rats. *Am J Kidney Dis* 28:878–887, 1996
16. Narita I, Ketteler M, Border WA, Noble NA: Nitric oxide mediates immunological injury to kidney mesangium in experimental glomerulonephritis. *Lab Invest* 72:17–24, 1995
17. Reyes AA, Purkerson ML, Karl I, Klahr S: Dietary supplementation with L-arginine ameliorates the progression of renal disease in rats with subtotal nephrectomy. *Am J Kidney Dis* 20:168–76, 1992
18. Peters H, Border WA, Noble NA: Tandem antifibrotic actions of L-arginine supplementation and low protein diet during the repair phase of experimental glomerulonephritis. *Kidney Int* 57:992–1001, 2000