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Editorial Comments

The kidney and cardiovascular risk

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Introduction

A defective capacity to handle the sodium content in the diet seems to be the mechanism underlying a renal origin of arterial hypertension [1]. Different theories have tried to explain this mechanism, but the most plausible cause for the derangement in the renal capacity to excrete sodium is the presence, from the very early stages of the process, of renal vasoconstriction that facilitates sodium retention [2]. This vasoconstriction probably does not represent an intrinsic renal defect, but is the renal consequence of the systemic vascular adaptation to the hypertensive process [3]. This possibility does not exclude the pivotal role of the kidney in the development of hypertension, neither does it exclude the hypothesis that the increase in blood pressure is needed to maintain glomerular filtration rate and sodium excretion within normal limits [4]. Interestingly, renal vasoconstriction is functional in the initial stages of the disease and remains constant thereafter as a consequence of the nephrosclerosis secondary to persistently elevated blood pressure [5].

Arterial hypertension leads to renal insufficiency via two possible pathways [6]. The traditional view is that arterial hypertension produces renal failure as a consequence of glomerular ischaemia induced by damage to preglomerular arteries and arterioles, leading to progressive luminal narrowing and to a fall in glomerular blood flow. A complementary view is that hypertensive renal damage depends on transmission of the elevated systemic pressure to the glomeruli, inducing glomerular capillary hyperperfusion and hypertension, which in turn cause glomerular structural injury and progressive loss of renal function. In the absence of antihypertensive treatment, renal involvement was very frequent in primary hypertension. Perera described that proteinuria was present in 42%, and chronic renal failure in 18%, of a series of 500 patients followed until death by this author [7]. With the advent of antihypertensive therapy the cardiovascular prognosis of hypertensive patients improved dramatically, and renal prognosis has been considered by some authors as excellent when arterial hypertension is treated, with only a very small percentage of patients ($<2\%$) developing chronic renal failure [8,9]. However, some pieces of evidence indicate that the prognosis of renal function is not so good in essential hypertensive patients; among these are the increasing prevalence of nephrosclerosis as a cause of end-stage renal failure in patients entering dialysis programmes in both US and Europe [10,11], the existence of a progressive decline in renal function in a significant percentage of treated hypertensive patients [12–14], the association between blood pressure and serum creatinine consistent with the possibility that blood pressure elevations even below the hypertensive range may induce early renal damage [15], the description that in the United States one in 13 persons (7.7%) with hypertension will develop hypercreatininaemia [16], and finally the presence of proteinuria in percentages oscillating between 4 and 16% in different series of treated hypertensive patients [17]. All these arguments indicate that renal damage is still prevalent in essential hypertension, even considering that serum creatinine is a poor method of estimating the evolution of renal function, specially in the initial stages of chronic renal failure.

Relationship between renal damage and cardiovascular disease in primary hypertension

It is well known that the cardiovascular system is profoundly affected by the presence of advanced renal failure. In fact patients undergoing maintenance haemodialysis have a cardiovascular mortality approximately three times that of age-matched non-uraemic control subjects [18]. The increased mortality is associated with a higher frequency of atherosclerotic heart disease, myocardial infarction, left ventricular hypertrophy, and congestive heart failure [18]. Poor control of intravascular volume, arterial hypertension, and hyperlipidaemia are among the most relevant causes leading to cardiovascular death. In the case of primary

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hypertension, the correlation between renal damage and an increased rate of cardiovascular death seems to exist since the early stages of renal damage. In this sense the Hypertension Detection and Follow-up Program showed that baseline serum creatinine had a significant prognostic value for 8-year mortality [19]. For persons with serum creatinine concentration above 1.7 mg/dl, mortality was more than three times higher when compared to that of all other participants. These data indicate that although the incidence of clinically relevant hypercreatininaemia in a hypertensive population is low, an elevated serum creatinine is a potent independent risk factor for mortality [19]. The presence of proteinuria is also a potent predictor of a higher risk for cardiovascular morbidity and mortality [17].

Hypertensive subjects examined at autopsy are often found to have nephrosclerosis [20,21]. This condition is characterized by the presence of hyalinization of arterioles and by fibroplastic intimal thickening of small arteries. The association between these microvascular abnormalities and hypertension in viscera other than the kidney is usually said to be weak or absent [22,23]. Interestingly, it has been described that subjects with coronary heart disease exhibit greater hyalinization of renal arterioles than did matched control subjects [24]. Furthermore, in autopsy studies the presence of hyalinization in the renal arterioles has been shown to be a marker of the presence of advanced coronary atherosclerosis in otherwise asymptomatic young people [25].

Attention has been paid recently to the presence of microalbuminuria and its relevance as a predictor of cardiovascular disease [26]. The term microalbuminuria defines an abnormally elevated urinary albumin excretion in the absence of clinical proteinuria as measured by standard laboratory methods. Its prevalence in primary hypertension probably oscillates between 20 and 30% for untreated hypertensives and can be as high as 25% in treated patients. Microalbuminuria also is a predictor of cardivascular morbidity and mortality in diabetic and non-diabetic population. In primary hypertension it is also associated with factors that increase cardiovascular risk such as endothelial dysfunction, insulin resistance, hyperlipidaemia and higher body mass index [26]. Very recently it has been shown that the presence of microalbuminuria in primary hypertension correlates with a high cardiovascular risk [27]. It has been suggested that microalbuminuria represents the renal expression of a generalized disorder characterized by an increased endothelial permeability which may underlie the link between an increased urinary albumin excretion (UAE) and the elevated risk of cardiovascular disease [26]. On the other hand microalbuminuria has been shown to be a predictor for the appearance of overt diabetic nephropathy [26]; whether or not it is a predictor of renal function decay in primary hypertension remains to be confirmed, but some preliminary data seems to indicate that this could be the case [22,27–29].

Predictors of the development of nephrosclerosis

The increasing prevalence of nephrosclerosis and the increase in cardiovascular risk accompanying the existence of chronic renal failure from its mildest stages has led to the consideration that the identification of predictors of the future development of chronic renal failure would be of great clinical value. In this sense it has been described that in an urban population both glucose and systolic blood pressure control, particularly in males, decrease the frequecy of impaired renal function [30]. There is greater damage in the renal vessels of hypertensive patients presenting hyperuricaemia in the presence of a normal glomerular filtration rate [31]. Furthermore the presence of hyperuricaemia seems to be linked to a worse renal outcome at equal levels of blood pressure control [12]. The elevated prevalence of hyperuricaemia in previously untreated hypertensive populations makes this finding of interest, because elevated levels of uric acid are a characteristic of the so-called syndrome X [32] characterized by the presence of insulin resistance and hyperinsulinism that contribute to increase cardiovascular morbidity and mortality significantly. In our experience [33] nephrosclerosis was accompanied by higher initial levels of both systolic and diastolic blood pressure, a predominant male gender, higher initial levels of serum uric acid and triglycerides, and lower levels of HDL cholesterol. Furthermore, it has been recently shown that insulin resistance may predispose older mildly hypertensive subjects to renal injury by worsening renal hemodynamics through the elevation of of glomerular filtration fraction and resultant glomerular hyperfiltration [34]. All these data indicate that the metabolic alterations that are frequently associated with elevated blood pressure jointly facilitate the progression of atherosclerosis and of nephrosclerosis.

In summary, all this information allows us to propose that renal vascular damage produced by arterial hypertension runs in parallel with alterations of the systemic vascular function and structure, to which cardiovascular morbidity and mortality are attributed. As a consequence of this concept, alterations of renal function have to be considered closely when stratifying for cardiovascular risk in studies in hypertensive patients. When deranged renal function is present, these findings necessitate therapeutic intervention.

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References

1. de Wardener HE. The primary role of the kidney and salt intake in the etiology of essential hypertension: part I. *Clin Sci* 1990; 79: 193–200
2. Ruilope LM, Lahera V, Rodicio JL, Romero JC. Are renal hemodynamics a key factor in the development and maintenance of arterial hypertension in humans? *Hypertension* 1994; 23: 3–9
3. Folkow B. Kidneys in primary hypertension—Initiators, stabilizers or/and victim-aggravators? *Blood Pressure* 1994; 3: 212–215
4. Ruilope LM. How much does the kidney participate in the origin of primary hypertension? *Blood Pressure* 1994; 3: 216–218

5. Ruilope LM, Campo C, Rodicio JL. Relationship between blood pressure and renal function. *J Hypertens* 1994; 12 [Suppl 8]: S55–S59
6. Baldwin DS, Neugarten J. Blood pressure control and progression of renal inssufficiency. *Contemp Issues Nephrol* 1986; 14: 81–110
7. Perera GA. Hypertensive vascular disease: description and natural history. *J Chronic Dis* 1995; 1: 33–42
8. Weisstuch JM, Dworkin LD. Does essential hypertension cause end-stage renal failure? *Kidney Int* 1992; 41 [Suppl 36]: S33–S37
9. Madhavan S, Stockwell D, Cohen H, Alderman MH. Renal function during antihypertensive treatment. *Lancet* 1995; 345: 749–751
10. National Institute of Diabetes and Digestive and Kidney Diseases. *US Renal Data System: Annual Data Report*. Bethesda, Maryland: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, 1989
11. Ruilope LM, Alcázar JM, Rodicio JL. Renal consequences of arterial hypertension. *J Hypertens* 1992; 10 [Suppl 7]: S85–S90
12. Ruilope LM, Alcázar JM, Hernández E, Moreno F, Martínez MA, Rodicio JL. Does an adequate control of blood pressure protect the kidney in essential hypertension. *J Hypertens* 1990; 8: 525–532
13. Rostand SG, Brown G, Kirk K, Rutsky EA, Dustan HP. Renal insufficiency in treated essential hypertension. *N Engl J Med* 1989; 320: 684–688
14. Rosansky SJ, Hoover DR, King I, Gibson J. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Arch Intern Med* 1990; 150: 2073–2076
15. Perneger TV, Nieto FJ, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine. Results from the 'Clue' Study and the ARIC Study. *JAMA* 1993; 269: 488–493
16. Perneger TV, Klag MJ, Feldman HI, Whelton PK. Projections of hypertension-related renal disease in middle-aged residents of the United States. *JAMA* 1993; 269: 1272–1277
17. Samuelsson O. Hypertension in middle-aged man: management, morbodity and prognostic factors during long-term hypertensive care. *Acta Med Scand [Suppl]* 1985; 702: 1–79
18. Rostand SG, Brunzell JD, Cannon RO, Victor RG. Cardiovascular complications in renal failure. *J Am Soc Nephrol* 1991; 2: 1053–1058
19. Shulman NB, Ford CE, Hall WD *et al*. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the Hypertension Detection and Follow-up Program. *Hypertension* 1989; 13 [Suppl I]: I-80–I-93
20. Takazakura E, Sawabu N, Handa A, Takada A, Shinoda A, Takeuchi J. Intrarenal vascular changes with age and disease. *Kidney Int* 1972; 2: 224–230
21. Tracy RE, Bhandaru SY, Oalmann MC, Guzmán MA, Newman WP III. Blood pressure and nephrosclerosis in black and white men and women aged 25 to 54. *Mod Pathol* 1991; 4: 602–609
22. Moritz AR, Oldt MR. Arteriolar sclerosis in hypertensive and non-hypertensive individuals. *Am J Pathol* 1963; 43: 273–299
23. Tracy RE, Johnson WD, López CR, Toca VT. Hypertension and arteriolar sclerosis of the kidney, pancreas, adrenal gland, and liver. *Virchow Arch* 1981; 391: 91–106
24. Tracy RE, Malcom GT, Oalmann MC, Newman WP III, Guzman MA, Strong GP. Nephrosclerosis in coronary heart disease. *Mod Pathol* 1994; 7: 301–309
25. Tracy RE, Strong JP, Newman III WP, Malcom GT, Oalmann MC, Guzman MA. Renovasculopathies of nephrosclerosis in relation to atherosclerosis at ages 25–54 years. *Kidney Int* 1996; 49: 564–570
26. Ruilope LM, Rodicio JL. Microalbuminuria in clinical practice. *Kidney: A Current Survey of World Literature* 1995; 4: 211–216
27. Agrawal B, Berger A, Wolf K, Luft FC. Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. *J Hypertens* 1996; 14: 223–228
28. Minram A, Ribstein J, DuCalair G. Is microalbuminuria a marker of early intrarenal vascular dysfunction in essential hypertension? *Hypertension* 1994; 23 [Part 2]: 1018–1021
29. Cerasola G, Cottone S, Mule G *et al*. Microalbuminuria, renal dysfunction and cardiovascular complication in essential hypertension. *J Hypertens* 1996; 14: 921–926
30. Tierney WM, Harris LE, Copley JB, Luft FC. Effect of hypertension and type II diabetes on renal function in an urban population. *Am J Hypertens* 1990; 3: 69–75
31. Messerli FH, Fhrolich ED, Dreslinski GR, Suarez DH, Aristimuno CG. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med* 1980; 93: 817–821
32. Reaven GM, Lithell H, Landsberg L. Mechanisms of disease: hypertension and associated metabolic abnormalities—The role of insulin resistance and the sympathoadrenal system. *N Engl J Med* 1996; 334: 374–381
33. Ruilope LM, Alcázar JM, Hernández E *et al*. Metabolic alterations accompanying essential hypertension are associated with nephrosclerosis. *J Hypertens* 1993; 11 [Suppl 5]: S475 (abstract)
34. Dengel DR, Goldberg AP, Mayuga RS, Kairis GM, Weir MR. Insulin resistance, elevated glomerular filtration fraction, and renal injury. *Hypertension* 1996; 28: 127–132

Dietary salt intake and left ventricular hypertrophy

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Introduction

In recent years the effects of dietary salt intake on blood pressure have been extensively examined. Traditionally studies have analysed to what extent blood pressure increases with high salt intake and decreases with salt restriction, and which subpopulation is most sensitive to salt loading and restriction respectively. In this paper we focus on the effects of dietary salt intake on hypertensive target organ damage beyond its potential effect on blood pressure [1], in particular on left ventricular hypertrophy.

Left ventricular hypertrophy

In the early stages of arterial hypertension, the development of left ventricular hypertrophy represents a structural adaptation of the myocardium to persistent pressure overload. Data from several studies docu-

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mented that left ventricular hypertrophy diagnosed either by electrocardiography or echocardiography offers prognostic information beyond that provided by evaluation of traditional cardiovascular risk factors. According to the Framingham Heart Study, evidence of left ventricular hypertrophy was associated with a 3- to 15-fold increased rate of cardiovascular events, such as cardiac failure, myocardial infarction, cardiac sudden death, and stroke [2]. In patients with coronary artery disease it was shown that left ventricular hypertrophy worsens survival in patients after myocardial infarction and increases the incidence of new cardiac events and of atherothrombotic brain infarction.

Eighty to ninety per cent of patients with end-stage renal disease have secondary arterial hypertension. A high prevalence of left ventricular hypertrophy has been demonstrated and subsequent prospective studies found that in hypertensive patients with end-stage renal disease left ventricular mass and geometry have a major effect on mortality [3]. Thus, left ventricular hypertrophy has been clearly identified as a surrogate endpoint for cardiovascular morbidity and mortality and to be more meaningful than blood pressure alone, since it predicted cardiovascular complications in patients with hypertension and in the general population more closely than any other traditional cardiovascular risk factor with the exception of age [2].

The development of left ventricular hypertrophy is not solely linked to an increase in afterload or wall stress. In mild-to-moderate arterial hypertension the degree of left ventricular hypertrophy is in part determined by non-haemodynamic factors as well, whereas only in severe and malignant hypertension a straightforward relationship is found between pressure load and left ventricular hypertrophy. Dietary salt intake may modify the process of myocardial hypertrophy either directly by increasing arterial pressure or indirectly by non-haemodynamic mechanisms [4].

Salt intake and blood pressure

In the INTERSALT study, in 10 079 men and women aged 20–59 years of 32 countries and 52 population samples, dietary salt intake as measured by 24-h urinary sodium excretion was modestly related to blood pressure across populations and within populations [5]. Data of the INTERSALT-study indicate that a sodium intake lower by 100 mmol—for example 70 instead of 170 mmol per day—results in a systolic blood pressure reduction by 3 mmHg. Furthermore the increase in systolic blood pressure with age, e.g. from 25 to 55 years, was diminished by 10 mmHg according to the INTERSALT data, if sodium intake was lowered by 100 mmol [5]. A thorough meta-analysis of randomized controlled clinical trials found rather disappointing blood pressure changes with salt restriction. The decrease in blood pressure for a 100 mmol/day reduction in daily sodium excretion was 3.7 mmHg for systolic and 0.9 mmHg for diastolic in the hypertensive patients and 1.0 mmHg systolic and 0.1 mmHg diastolic in the normotensive subjects [6]. The blood pressure response to dietary sodium restriction, however, was considerably augmented in trials of hypertensive subjects with a mean age of 45 years or older [6]. In the majority of patients with secondary hypertension removal of excessive salt and water by dialysis combined with dietary restriction of salt and water intake leads to a decrease in blood pressure and better control of arterial hypertension. Thus dietary salt intake may cause a significant decrease in blood pressure in some patients, in particular in older patients and in those with secondary hypertension, who are relatively salt sensitive. Unfortunately clinical tests cannot predict whether a hypertensive patient is salt sensitive or not. Since blood pressure reduction determines regression of left ventricular hypertrophy [7], dietary salt intake may reduce left ventricular hypertrophy by decreasing the haemodynamic load or wall stress of the left ventricle.

Dietary salt intake and left ventricular hypertrophy

In 1988 we first reported a close relationship between 24-h urinary sodium excretion (as an estimate of salt intake) and left ventricular mass in mild-to-moderate essential hypertension, with sodium excretion being an independent and more powerful determinant of left ventricular mass than even blood pressure [8]. Several research groups in different countries have confirmed a relationship between dietary salt intake and left ventricular hypertrophy, which was independent of blood pressure. This was found irrespective of whether dietary salt intake was assessed with the help of a trained dietician or using 24-h urinary sodium excretion as an estimate [4]. Moreover, diastolic dysfunction of the left ventricle often precedes the development of left ventricular hypertrophy; diastolic left ventricular dysfunction was also related to 24-h urinary sodium excretion in hypertensive patients [9]. Stepwise multiple regression analysis confirmed that sodium intake was the strongest determinant of diastolic filling, independent of left ventricular size, heart rate, and ambulatory blood pressure [9].

All available data were obtained in patients with essential hypertension. No data are available on the impact of sodium intake and left ventricular hypertrophy in secondary hypertension or in end-stage renal disease. It is intriguing to speculate that the sodium balance determines left ventricular structure in patients on chronic haemodialysis as well, independent of blood pressure.

So far the data do not permit the determination of whether the relation between dietary salt intake and left ventricular hypertrophy reflects a cause–effect relationship. Experimental data in rats and therapeutic studies in humans support the notion that dietary salt intake induces myocardial hypertrophy independent of haemodynamic load conditions [4]. Results from two clinical studies suggest a parallel decline of salt intake and left ventricular mass: After 12 months of sodium restriction left ventricular mass decreased by 5.4% in 76 previously untreated subjects with uncomplicated

mild-to-moderate hypertension and by 8.6% in patients with left ventricular hypertrophy, according to echocardiographic criteria [10]. The explanatory power of dietary intervention with respect to change in left ventricular mass decreased when sodium restriction and change in arterial pressure were included in the multivariate regression analysis [10]. The decrease in left ventricular mass in patients with left ventricular hypertrophy was comparable to that seen with most but not all antihypertensive drugs [7]. The Treatment of Mild Hypertension Study Research Group showed a significant correlation between reduced salt intake and left ventricular mass independent of other covariates including blood pressure. In the whole study group salt restriction was the only factor significantly correlated with reduction in left ventricular mass; notably this was not found for the decrease in blood pressure [4].

Pathogenetic mechanisms of sodium-induced left ventricular hypertrophy

In addition to the potential effects of dietary salt intake on blood pressure and thereby on left ventricular hypertrophy, other mechanisms of how sodium could effect left ventricular structure need to be discussed. First, and this may be most important for patients on chronic haemodialysis, intracellular sodium concentrations play an important role in adaptation of the left ventricular muscle to a persistent increase in blood pressure. Among various parameters, intracellular sodium and calcium concentrations were found to be significantly correlated with the degree of left ventricular hypertrophy in humans [11]. Of note is the fact that the sodium and not the anion (such as chloride) influences the process of left ventricular hypertrophy. Alternatively, high salt intake may increase left ventricular end-diastolic volume, a parameter reflecting cardiac preload. However, an independent relationship of left ventricular end-diastolic diameter to urinary sodium excretion was found only in a single study [4].

Sodium has multiple links with the renin–angiotensin–aldosterone system. Angiotensin II is known to modify myocardial growth according to various experimental studies. Conversely, blocking of angiotensin II synthesis by ACE-inhibitors is significantly more effective in reducing left ventricular hypertrophy in patients with essential hypertension than are diuretics or beta-blockers [7]. Most recently we investigated the interaction of angiotensin II with sodium excretion on left ventricular structure in mild-to-moderate essential hypertension. Patients with high plasma angiotensin II concentrations in relation to their sodium excretion had greater posterior wall thickness and greater left ventricular mass than patients with lower levels of angiotension II [12]. Thus inadequate suppression of angiotensin II in response to high dietary salt intake in some hypertensive patients seems to aggravate left ventricular hypertrophy.

Dietary salt intake could also exert trophic actions on the myocardium via the sympathetic nervous system, since the activity of the sympathetic nervous system is influenced by the sodium balance. In this context it is of note that in some hypertensive patients high salt intake stimulates the sympathetic nervous system instead of suppressing it as in normal individuals. So far, however, convincing evidence that sympathetic activity mediates the cardiotrophic effects of sodium is missing.

At present the best candidates for the modulating impact of dietary salt intake on left ventricular hypertrophy in human arterial hypertension are (i) a direct action of intracellular sodium content of the myocardial cells, and (ii) growth stimulating actions of angiotensin II, assuming that in some hypertensive patients high salt intake causes inadequate suppression of ANG II [12].

Salt restriction: yes or no?

The endless discussion of whether dietary salt restriction leads to a substantial and clinically relevant reduction in blood pressure may be besides the point. We now have increasing evidence that dietary salt intake influences hypertensive target organ damage, in particular left ventricular hypertrophy, independently of blood pressure. Left ventricular mass reflects the average blood pressure load on the cardiac system more closely than even ambulatory blood pressure recordings. The tight and independent correlation of dietary salt intake with left ventricular hypertrophy further strengthens the case that dietary sodium is a widespread perpetrator of cardiovascular disease. These considerations are particularly pertinent in such patients who are characterized by substantial sodium retention.

Sodium restriction was found to reduce the degree of left ventricular hypertrophy in parallel with blood pressure reduction, but such reduction could not be fully explained by the decrease in arterial pressure. These first therapeutic studies are in good agreement with current pathogenetic concepts that dietary salt intake modifies the myocardial hypertrophic response to a persistent pressure load. At present there is increasing evidence to recommend sodium restriction in hypertensive patients with left ventricular hypertrophy. The response rate and magnitude of reduction of left ventricular hypertrophy to dietary salt restriction is unknown. Further work is required to define potential subgroups who would profit most from such dietary intervention.

References

1. Antonios TFT, MacGregor GA. Salt—more adverse effects. *Lancet* 1990; 348: 250–251
2. Levy D, Garrison RJ, Savage DD *et al.* Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; 332: 1561–1566
3. Foley RN, Parfrey PS, Hamet JD *et al.* Prognostic importance of left ventricular hypertrpohy in uremic cardiomyopathy. *J Am Soc Nephrol* 1995; 5: 2024–2031
4. Schmieder RE, Beil AM: Salt intake and cardiac hypertrophy. In: JH Laragh, BM Brenner (eds): *Hypertension: Pathophysiology, Diagnosis and Management*, 2nd edn. Raven Press, New York, 1995;1327–1333

5. Elliott P, Stamler J, Nichols R *et al.*: Intersalt revisited: further analysis of 24 hour sodium excretion and blood pressure within and across populations. *Br Med J* 1996; 312: 1249–1253
6. Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium and blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996; 275: 1590–1597
7. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double blind trials. *JAMA* 1996; 275: 1507–1513
8. Schmieder RE, Messerli FH, Garavaglia GE, Nunez BD. Dietary salt intake: a determinant of cardiac involvement in essential hypertension. *Circulation* 1988; 78: 951–956
9. Langenfeld MRW, Schmieder RE, Schobel HP, Friedrich A. *Dietary salt intake and left ventricular diastolic function in early essential hypertension.* International Society of Hypertension, Glasgow 1996 (abstract)
10. Jula AM, Karanko HM. Effects on left ventricular hypertrophy of long-term nonpharmacological treatment with sodium restriction in mild to moderate essential hypertension. *Circulation* 1994; 89: 1023–1031
11. lnoue I, Matsumura H, Stringer T *et al.* Role of intracellular cation abnormality in development of left ventricular hypertrophy. *J Cardiovasc Pharmacol* 1991, 17 [Suppl. 2]: 107–109
12. Schmieder RE, Langenfeld MRW, Friedrich A, Schobel HP, Gatzka CD, Weihprecht H. Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. *Circulation* 1996; 94: 1393–1398

Bacterial infections in diabetes mellitus: are calcium channel blockers beneficial?

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In this issue Seyrek *et al.* [1] report that the calcium channel blocker amlodipine prevents and reverses elevation of intracellular calcium $[Ca^{2+}]_i$ and abnormal phagocytosis of polymorphonuclear leucocytes (PMNL) in diabetic rats. Why is this information potentially relevant for the clinical nephrologist ?

In the USA and in some European countries, renal failure in diabetic patients has become the single most frequent cause of end-stage renal failure [2,3]. Mortality in diabetic patients on dialysis is still excessively high. Bacterial infection is a common cause of death in the dialysed patient and this is particularly true for the diabetic patient on dialysis. Consequently it is obvious that procedures which have the potential to ameliorate impaired host defence mechanisms are of interest in clinical nephrology.

It must be emphasized that in the management of the diabetic patient all efforts should primarily be directed at achieving near normal glycaemia. Everyone involved in the management of diabetic patients knows that this ideal goal may not always be achieved. It is for this reason that ancillary interventions of proven clinical efficacy are indeed most welcome.

In an elegant series of studies [4,5] the Los Angeles team had previously documented that $[Ca^{2+}]_i$ is elevated in PMNL of patients with type II diabetes, similar to what had been shown for platelets of diabetic patients [5]. This abnormality was associated with impaired phagocytosis of oil red droplets and decreased concentration of ATP in PMNL. Such abnormal functions were normalized when the oral antidiabetic agent gliboride was administered to improve glycaemic control [4]. More recent studies [5] documented that glucose activates G-proteins, stimulates the adenylate cAMP protein kinase A pathway as well as the phopsholipase C system and affects transmembrane calcium influx. This reaction may not be specific for glucose, since the same effect could also be elicited using choline [1]. It appears that the above sequence is mediated via cell shrinkage induced by osmotic forces. Nevertheless the *in vivo* observations [5] document that, irrespective of it's specificity, the phenomenon may have potential clinical importance.

Why should increased intracellular calcium interfere with phagocytic activity?

It has been proposed that increased $[Ca^{2+}]_i$ of resting PMNL of diabetic patients are associated with a subnormal increase in $[Ca^{2+}]_i$ after several stimulatory manoeuvres. Normalization of resting $[Ca^{2+}]_i$ was associated with normalization of $[Ca^{2+}]_i$ kinetics [6].

Bacterial defence by PMNL is incredibly complex and involves numerous, partially unrelated, steps [6]. When nature armed PMNL for this task, she obviously did not put all eggs into one single basket. This may explain why there is so much redundance in this system. The question also arises whether changes in oil-droplet phagocytosis are an adequate surrogate for host defence. Despite this note of caution the assay measuring ingestion of opsonized oil red O containing oil-droplets coated with *Escherichia coli* lipopolysaccharide, as used by Seyrek *et al.* [1], undoubtedly interrogates an important step in host defence.

Do these findings relate to host defence in diabetic patients ? In view of the complexity of the antibacterial function of PMNL, phagocytosis of oil-droplets may not necessarily reflect the complete spectrum of anti-

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bacterial host defense adequately. When extrapolating from *in vitro* to *in vivo,* many investigators had unpleasant surprises. It has yet to be shown that reversing $[Ca^{2+}]_i$ of PMNL in diabetic rats by the calcium channel blocker amlodipine does indeed improve the host defence against experimental bacterial infections using hard endpoints e.g. survival. Such evidence is required before far reaching clinical recommendations can be drawn from the undoubtedly interesting observation of Seyrek *et al.* [1].

In this context one point relating to the mechanism of action of calcium channel blockers deserves comment. It is uncertain whether PMNL have L-type calcium channels at all [7]. This raises the possibility that one is dealing with non-classical actions of calcium channel blockers which are unrelated to their interaction with L-type calcium channels. This is reminiscent of findings of Orth *et al.* [8] who noted that enantiomers of calcium channel blockers which did not strongly interact with the L-type calcium channels were as active in inhibiting proliferation of adult human mesangial cells as were their stereoisomeres which strongly interacted with L-type calcium channels. Mesangial cell exhibit L-type calcium channels [8], but even more illustrative are experiments in endothelial cells which are devoid of L-type calcium channels in patch clamp studies [H. Haller, Berlin; personal communication]. Even in these cells calcium channel blockers interfere with a number of important activation steps mediated via PKC.

Recently, calcium channel blockers have become something of a pharmacological four letter word [9], although this attitude is based on extremely shaky evidence which does not hold water [10]. Against this background it is of particular interest that calcium channel blockers do not only have antihypertensive actions [11] and beneficial effects on progression of renal failure in experimental [12,13] and clinical [14,15] studies, but possibly also additional beneficial effects as suggested by the study of Seyrek *et al.* [1] in this issue.

References

1. Seyrek N, Marcinowski W, Smogorzewski M, Demerdash TM, Massry SG. Amlodipine prevents and reverses the elevation in $[Ca^{2+}]_i$ and the impaired phagocytosis of PMNL of diabetic rats. *Nephrol Dial Transplant* 1996; 12: 265–272
2. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. *Am J Kidney Dis* 1996; 27: 167
3. Lippert J, Ritz E, Schwarzbeck A, Schneider P. The rising tide of end-stage renal failure from diabetic nephropathy type II—an epidemiological analysis. *Nephrol Dial Transplant* 10;1995 462–467
4. Alexiewicz JM, Kumar D, Smogorzewski M, Klin M; Massry SG. Polymorphonuclear leucocytes in non-insulin-dependent diabetes mellitus: abnormalities in metabolism and function. *Ann Intern Med* 1995; 123: 919–924
5. Demerdash TM, Seyrek N, Smogorzewski M, Marcinkowski W, Nasser-Moadelli S, Massry SG. Pathways through which glucose induces a rise in $[Ca^{2+}]_i$ of polymorphonuclear leucocytes of rats. *Kidney Int* 1996; 50: 2032–2040
6. Goetz MB, Proctor RA. Normalization of intracellular calcium: A sweet solution to neutrophil dysfunction in diabetes? *Ann Intern Med* 1995; 123: 952–954
7. Tsien RW, Tsien RY. Calcium channels, stores and oscillation. *Ann Rev Cell Biol* 1990; 6: 715–760
8. Orth SR, Nobiling R, Bönisch S, Ritz E. Inhibitory effect of calcium channel blockers on human mesangial cell growth: Evidence for actions independent of L-type Ca^{2+} channels. *Kidney Int* 1996; 49: 868–879
9. Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; 92:1 326–1331
10. Messerli FH. Are calcium antagonists safe? *Lancet* 1995; 346: 767–768
11. Epstein M. Calcium antagonists in the management of hypertension. In: Epstein M, ed. *Calcium antagonists in clinical medicine*. Hanley & Belfus, Philadelphia, 1992: 213–230
12. Münter K, Hergenröder S, Jochims K, Kirchengast M. Individual and combined effects of verapamil and trandolapril on attenuating hypertensive glomerulopathic changes in the stroke-prone rat. *J Am Soc Nephrol* 1996; 7: 681–686
13. Harris DCH, Hammond WS, Burke TJ, Schrier RW. Verapamil protects against progression of experimental chronic renal failure. *Kidney Int* 1987; 31: 41–46
14. Bakris GL, Copley JB, Vickmair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 1996; 50: 1641–1650
15. Zuchelli P, Zuccalà A, Borghi M *et al.* Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. *Kidney Int* 1992; 36: 452–458

ANCA-positive vasculitis and alpha 1-antitrypsin deficiency: could free ANCA antigens released by neutrophils mediate vasculitic lesions?

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Antineutrophil cytoplasmic antibodies (ANCA) are implicated in the pathogenesis of necrotizing vasculitis affecting small vessels (arterioles, capillaries, and venules), particularly in Wegener's granulomatosis and microscopic polyangiitis (MPA). The main antigenic targets for ANCA are proteinase 3 (PR3) and myeloperoxidase (MPO). ANCA have been implicated in pathogenesis since titres have shown a correlation with

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disease activity and rise before clinical relapses. The current hypothesis for the ANCA pathogenetic mechanism is that these autoantibodies induce neutrophil activation leading to the release of toxic proteases (including PR3) and reactive oxygen species (ROS, the most active being generated by MPO) which could induce the observed vasculitic lesions. Free PR3 [1] and MPO [2] are found at the site of vasculitic lesions in ANCA-positive crescentic glomerulonephritis. Recent data suggest an additional mechanism for 'ANCA-mediated vasculitis' i.e. the role of free ANCA antigen in the context of an acquired and/or genetically determined protease/antiprotease imbalance.

After neutrophil activation, the activity of the very powerful neutral serine proteases is normally tightly restricted to the inflammation site by a large excess of circulating antiproteases. Alpha 1-antitrypsin (α_1AT), the main inhibitor of neutral serine proteinase (elastase and PR3) [3,4] present in alpha granules of polymorphonuclear leukocytes, is encoded by a highly polymorphic gene with at least 75 alleles at the so-called protease inhibitor (PI) locus [4]. PI alleles may be classified as either normal (M) or deficient (Z) according to circulating α_1AT levels. Since the two parental alleles are codominantly expressed, homozygous PI-ZZ is a severely deficient, heterozygous PI-MZ a moderately deficient and PI-MM a normal α_1AT phenotype. Severe α_1AT deficiency is recognized as a risk factor for the development of panlobular emphysema and various hepatic disorders in children and adults as well as such autoimmune disorders as anterior uveitis, systemic lupus erythematosus, and neutrophilic ulcerative panniculitis. In adults with α_1AT deficiency, some isolated case reports have indicated the possible occurrence of systemic vasculitis and necrotizing glomerulonephritis. We first described the association between anti-PR3 ANCA activity and the deficient PI-ZZ phenotype in ANCA-positive systemic vasculitis [5], an observation now widely confirmed by others [6–9]. The exact incidence of deficient α_1AT phenotypes in ANCA-positive systemic vasculitis, which is currently under investigation in a large international collaborative study, is probably low in unselected patients. However, the clinical relevance of searching for antiprotease deficiency is emphasized by the poor outcome of anti-PR3-positive patients with the severely deficient PI-ZZ phenotype [10].

Furthermore, pathological conditions might lead to acquired localized antiprotease 'relative deficiency'. α_1AT is degraded in the context of acute respiratory distress syndrome [11], and in smokers at the site of inflammation in bronchoalveolar fluid [12]. *Pseudomonas aeruginosa* can promote an elastase/antielastase imbalance by increasing the release of neutrophil elastase and enhancing the oxidative inactivation of α_1AT [13]. *In vitro* experiments have shown that excessive neutrophil elastase can inactivate and cleave α_1AT, leading to the release of a 4.2 kD fragment with potent chemoattractant properties [14]. Such a condition, if observed *in vivo*, would lead to further influx of neutrophils and aggravation of protease/antiprotease imbalance. Reactive oxygen species can also oxidize and inactivate α_1AT, and MPO can produce hypochlorous acid, the most powerful ROS, which in turn can form long-acting chloramines. Since chronic ENT infection often precedes overt vasculitis, we postulate that acquired localized α_1AT inactivation may prevent the normal limitation of proteolytic activity after neutrophil activation, with spreading of the vasculitic lesions and exposure of the ANCA antigen to the immune system, allowing the generation of ANCA. Indeed, patients with limited vasculitis often do not have detectable ANCA, which will only appear at the time of overt systemic vasculitis.

Finally, ANCA may interfere with α_1AT inhibition of PR3 and contribute to the generation of a protease/antiprotease imbalance. Anti-PR3 antibodies from patients with active Wegener's granulomatosis inhibit PR3 proteolytic activity but also the complexing of PR3 with α_1AT. The inhibition of PR3 complexing with α_1AT by anti-PR3 antibodies could interfere with PR3 clearance. Residual anti-PR3/PR3 complexes may be pathogenic, since they retain some proteolytic properties and could act as a reservoir for PR3 after dissociation from its antibody counterpart. The inhibitory effect of anti-PR3 antibodies on PR3/α_1AT complexing is correlated more closely with disease activity than anti-PR3 levels in Wegener's granulomatosis [15]. The ability of anti-PR3 antibody to inhibit PR3 proteolytic activity might also correlate with disease activity, although some sera with anti-PR3 ANCA may not inhibit PR3/α_1AT complexing [16]. Therefore other studies are needed to improve our understanding of the complex interaction between PR3, anti-PR3 ANCA and α_1AT.

In conclusion, we suggest a role for free ANCA antigen in the pathogenesis of systemic vasculitis in the context of a protease/antiprotease imbalance, which could be either genetically determined in rare patients or more frequently acquired through α_1AT inactivation in various pathological conditions and possible inhibition of PR3/α_1AT complexing by anti-PR3 ANCA.

References

1. Mrowka C, Csernok E, Gross WL, Feucht HE, Bechtel U, Thoenes GH. Distribution of the granulocyte serine proteinases proteinase 3 and elastase in human glomerulonephritis. *Am J Kidney Dis* 1995; 25: 253–261
2. Saeki T, Kuroda T, Morita T, Suzuki K, Arakawa M, Kawasaki K. Significance of myeloperoxidase in rapidly progressive glomerulonephritis. *Am J Kidney Dis* 1995; 26: 13–21
3. Rao NV, Wehner NG, Marshall BC, Gray WR, Gray BH, Hoidal JR. Characterization of proteinase 3 (PR3), a neutrophil serine proteinase. *J Biol Chem* 1991; 266: 9540–9548
4. Brantly M, Nukiwa T, Crystal RG. Molecular basis of alpha 1-antitrypsin deficiency. *Am J Med* 1988; 84(6A): 13–31
5. Esnault VLM, Testa A, Audrain M *et al.* Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int* 1993; 43: 1329–1332
6. Elzouki ANY, Segelmark M, Wieslander J, Eriksson S. Strong link between the alpha 1-antitrypsin PiZ allele and Wegener's granulomatosis. *J Intern Med* 1994; 236: 543–548
7. Lhotta K, Vogel W, Meisl T *et al.* α1-antitrypsin phenotypes in

patients with anti-neutrophil cytoplasmic antibody-positive vasculitis. *Clin Sci* 1994; 87: 693–695
8. Savige JA, Chang L, Cook L, Burdon J, Daskalakis M, Doery J. α_1-Antitrypsin deficiency and anti-proteinase 3 antibodies in antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. *Clin Exp Immunol* 1995; 100: 194–197
9. Griffith ME, Lovegrove JU, Gaskin G, Whitehouse DB, Pusey CD. C-antineutrophil cytoplasmic antibody positivity in vasculitis patients is associated with the Z allele of alpha 1-antitrypsin, and P-antineutrophil cytoplasmic antibody positivity with the S allele. *Nephrol Dial Transplant* 1996; 11: 438–443
10. Segelmark M, Elzouki AN, Wieslander J, Eriksson S. The PiZ gene of α1 antitrypsin as a determinant of outcome in PR3-ANCA-positive vasculitis. *Kidney Int* 1995; 48: 844–850
11. Cochrane CG. Alpha 1-proteinase inhibitor in inflammatory states of humans and laboratory animals. *Am J Med* 1988; 84(6A): 75–79
12. Ogushi F, Hubbard RC, Vogelmeier C, Fells GA, Crystal RG. Risk factors for emphysema. Cigarette smoking is associated with a reduction in the association rate constant of lung α1-antitrypsin for neutrophil elastase. *J Clin Invest* 1991; 87: 1060–1065
13. Ras GJ, Theron AJ, Anderson R *et al*. Enhanced release of elastase and oxidative inactivation of α1-protease inhibitor by stimulated human neutrophils exposed to *Pseudomonas aeruginosa* pigment 1-hydroxyphenazine. *J Infect Dis* 1992; 166: 568–573
14. Banda MJ, Rice AG, Griffin GL, Senior RM. α1-proteinase inhibitor is a neutrophil chemoattractant after proteolytic inactivation by macrophage elastase. *J Biol Chem* 1988; 263: 4481–4484
15. Dolman KM, Stegeman CA, Van de Wiel BA *et al*. Relevance of classic anti-neutrophil cytoplasmic autoantibody (C-ANCA)-mediated inhibition of proteinase 3-α1-antitrypsin complexation to disease activity in Wegener's granulomatosis. *Clin Exp Immunol* 1993; 93: 405–410
16. Daouk GH, Palsson R, Arnaout MA. Inhibition of proteinase 3 by ANCA and its correlation with disease activity in Wegener's granulomatosis. *Kidney Int* 1995; 47: 1528–2536

A conceptual-methodological framework for a participatory use of the EDTA registry

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General framework

The specific interest, and possibly the uniqueness, of the EDTA registry resides in two of its institutional characteristics: it is one of the oldest clinical registries, and has been since the very beginning a large-scale, multinationally conceived, prospective database, proposed and managed by the clinical protagonists themselves, rather than dumped on them from the outside.

The world of the registries (their purposes and instruments) and the area to which registries belong—namely, epidemiology—have substantially evolved over the life-span of the EDTA. It should suffice to recall the many huge databases made possible by the boom in computerized techniques, the flourishing of specialized registries of transplants, the appearance of clinical epidemiology as a well-defined companion discipline of general epidemiology, and the multiplication of national and international programmes of quality of care and technology assessment in many fields of medicine and public health.

The EDTA registry has successfully expanded (not without some uneasiness, mainly over the last few years) in this changing world. It is expected, however, that a radical revision of the conceptual (not only of the material) framework of the original structure is needed. The purpose of this brief presentation is to outline the main criteria likely to be useful for such a revision, which can rely on the fact that the hardware and software architecture of the registry has been altered to ensure a friendly and powerful environment for data handling, potentially pliable to serve a large range of needs.

Background definitions

The conceptual backbone of the present proposals for a new life of the EDTA registry is drafted in Table 1, in which its philosophy and goals are contrasted with those of diseases/populations-based (or oriented) registries.

The population of the EDTA represents itself and the overall reality of dialysis and transplant only insofar as the centres voluntarily contributing to the registry represent the health care setting(s) of their country and provide complete and reliable information on their performance.

The classical data which epidemiologists collect and produce (mainly as 'external' experts) serve a different purpose from those provided by clinicians who chose to be also epidemiologists. The history of diseases within a population is provided as neutrally as possible by epidemiological studies and registries; the epidemiological cohorts generated by EDTA-like registries tell the history of the diseases in the perspective of, and mediated by, the patterns of care offered by the network of participating centres. The settings of care become a key element and a specific resource in the investigation and interpretation of the outcomes of

Table 1. Conceptual and methodological framework of the EDTA registry

	Registries of	
Diseases		*Interventions*
Populations	← based →	Practices
↓		↓
Incidence Prevalence Trends	only in →	'Qualified' populations
↓		↓
Scanning for causal associations risks↔events		• Comparative evaluation of • settings↔cohorts • Testing of well-defined hypotheses
↓		↓
Epidemiology Central specialized monitoring		• Clinical epidemiology • Outcome research • Network of 'participants'

interventions on the populations/diseases selected to constitute a 'clinical epidemiological' registry.

The specificity and the yield of the EDTA registry

As previously mentioned, the EDTA registry is specifically relevant for its duration and size. A further element of worth is the heterogeneity of the settings which it represents. The critical challenge is how to cross-fertilize these two characteristics, since heterogeneity is often seen as a weakness, if not a stumbling block. The key choice is to reconstruct within the general registry different sub-cohorts individually homogeneous and complete with respect to the specific hypotheses explored. This process can generate comparative series defined:

- by the length of follow-up (also implying different durations of exposure to different strategies of care);
- by prespecified diagnostic categories;
- by country of origin;
- by type of centre.

The only (intrinsic) requirement of a cohort is the completeness of the follow-up available for its member patients. The model could be applied both retrospectively, over the long span of existence of EDTA, and prospectively, formulating specific hypotheses, and actively involving and monitoring the centres most interested. The registry acts in this sense as a very powerful network, flexibly adapted to focus on predefined issues. The case of 'rare diseases' is by definition a model situation, as the accrual of cases over the years allows the availability of numerically important series. The end-product will not be incidence-prevalence data, albeit some knowledge on the natural history of the disease given the care provided in the various settings.

Specific areas of interest

The heterogeneous nature of the registry network and the unwonted wealth of comparative information it makes available across countries and world regions suggest two main areas of development.

One is that it would be important to generate *ad hoc* projects where epidemiological data could be enriched with informations specifically addressing aspects of health economics, with a possible emphasis on subthemes, such as treatment costs, impact of care settings, accessibility, or cost-effectiveness analyses. A sample of the registry data (appropriately integrated with the relevant data) could be periodically and cross-sectionally analysed; representative cohorts of patients and/or centres could be followed up and evaluated prospectively, to describe trends in care strategies and costs, as well as their (cultural and political) determinants.

Another area of possible intensive 'development' of the registry is the use of its data for educational training purposes. Because of its very nature, the registry cannot be merely nor mainly conceived as a file from which publications could occasionally be derived. The clinicians' participation in collecting data documenting their routine practice implies and requires a more interactive feed-back. At the same time, the likelihood that the registry may remain, or better still further develop, as a living reality depends on the growth within the nephrological community of a stronger and more disseminated epidemiological perspective. In each country, and possibly in inter-country initiatives, the data (their yield, the methodological problems they pose, the heterogeneity they testify, the interplay between clinical, organizational, cultural variables they document) could be used in regular and officially sponsored training courses. Two main results should be pursued: the creation within each country of a core group of clinicians with clinical–epidemiological perspective and expertise, who could act as cultural promoters of registry-linked activities, and the intensification and improvement of the use of the data for scientific publications.

Conclusions

A registry which aims at documenting and exploring the research potential of the clinical routine cannot survive successfully if it is felt mainly as an administrative duty of compliance with recommendations. Clinical epidemiology has entered the field of medicine as a stimulating way of looking at clinical practice as a semiexperimental setting where clinically relevant hypotheses could find insight and perspective. The EDTA registry provides a challenging opportunity for establishing creative links between the various components of care. A high profile research programme on the intensive use of the registry (retrospective as well as prospective, based on routinely collected data as

well as on *ad hoc* complementary protocols) could substantially contribute to the maturation of an epidemiologically minded clinical (and basic) research. The EDTA could in this sense provide original insight, and contribute to the many developing registries and networks.

Perfusion storage versus static storage in kidney transplantation: is one method superior to the other?

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Key words: static storage; perfusion storage

Ischaemic injury to the renal allograft prior to revascularization is an important cause of delayed graft function which has been shown to correlate with decreased 1-year graft survival [1,2]. Flushing the kidney with hypothermic solution of intracellular electrolyte composition [3] minimizes the *ex vivo* injury. Cooling diminishes metabolic activity and decreases the oxygen demand of the preserved organ although metabolism still proceeds. In clinical practice kidneys are preserved either in static storage immersed in preservation solution at 0–4 C or in perfusion storage. During perfusion storage kidneys receive continuous or pulsatile flow at 4–10 C with preservation solution which supplies metabolites and dilutes metabolic end products. Lindbergh and Carrel developed kidney perfusion in 1938 [4]. Belzer *et al.* [5] in 1967 preserved canine kidneys for 3 days using continuous perfusion. There has been a reduction in the number of grafts preserved in perfusion storage from approximately 50% in 1981 to 10% in 1991 [6]. Static storage is simpler and less costly than perfusion storage but there is controversy in the literature regarding the effect of the preservation method in graft function.

Gregg *et al.* [7] in 1986 compared the function of autotransplanted kidneys in dogs preserved for 24 h in perfusion storage or static storage. Early graft function as measured by creatinine clearance, PAH clearance, and sodium reabsorption was better for kidneys preserved in perfusion storage; however, this advantage did not persist beyond the first month post-transplant. In a prospective randomized study from nine Ontario transplant centres, Halloran *et al.* [8] reported that the need for post-transplant dialysis, the 1-year graft, and patient survival and the incidence of grafts that never functioned was not different for kidneys preserved in static storage versus perfusion storage. In the study of Merion *et al.* [9] one kidney from one donor was preserved in static storage and the other in perfusion storage. The need for dialysis postoperatively and the serum creatinine levels at days 1, 7 and 30 post-transplant were not significantly different between the two groups. Prolonged cold ischaemia was associated with higher rate of dialysis requirement in both groups without a statistically significant difference between them. Contrary to this observation, Barber *et al.* [10] reported an immediate reduction in the post-transplant dialysis requirement from 31.3 to 7.8% by the use of perfusion storage as opposed to static storage. Likewise, Alijiani *et al.* [11] found that post-transplant dialysis was necessary in 17% of patients who received kidneys preserved in perfusion storage and in 63% of patients who received kidneys preserved in static storage. The length of cold ischaemia time was identified as a significant factor in the report of Jaffers and Banowsky [12]. The incidence of acute tubular necrosis increased in grafts preserved for more than 24 h in static storage as compared to grafts preserved in perfusion storage.

Zhou and Cecka [6] analysed the data from the UNOS and UCLA Transplant Registry and reported that from 1980 to 1991 no difference was found in 1-year graft survival or prevalence of delayed graft function between renal allografts preserved in perfusion storage *versus* static storage but there are no prospective randomized studies comparing long-term graft survival of kidneys preserved with either preservation method.

One potential advantage of perfusion storage is the evaluation of the renal allograft. Tesi *et al.* [14] found that pump parameters (flow and renal resistance) are useful as a quantitative means to determine the suitability of a renal allograft for transplant. This could help expand the donor pool with non-heart-beating donors.

To conclude, it seems that use of perfusion storage can contribute to a decreased delayed graft function rate, especially with prolongation of cold ischaemia time. There is no evidence that this beneficial effect alters long-term graft survival. Nevertheless, improved early graft function can have a significant impact on the cost of transplantation, and additionally, flow characteristics can assist in a more accurate assessment of the graft prior to the procedure.

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References

1. Terasaki PI *et al.* UCLA and UNOS registries. Overview. In: Terasaki PI, Cecka JM (eds). *Clinical Transplants*. UCLA Tissue Typing Laboratories, Los Angeles, CA, 1991; 409–430
2. Cacciarelli T, Sumrani N, Delaney V, Hong JH. The influence of delayed renal allograft function on long term outcome in the cyclosporine era. *Clin Nephrol* 1993; 39(6): 335–339
3. Collins GM, Green RD, Halasz NA. Importance of anion content and osmolarity in flush solutions for 48 to 72 hr hypothermic kidney storage. *Cryobiology* 1979; 16: 217
4. Carrel A, Lindbergh CA. In: The Culture of organs. Hamish Hamilton, London 1938; 221
5. Belzer FO, Ashby BS, Dunnphy JE. 24 hour and 72 hour preservation of canine kidneys. *Lancet* 1967; 2: 536–539
6. Zhou YC, Cecka JM. Preservation. In: Terasaki PI, Cecka JM (eds). *Clinical Transplants*. UCLA Tissue Typing Laboratory, Los Angeles, California 1992; 383–390
7. Gregg CM, Cos LR, Sarf P, Fridd CW, Linke CA. Recovery of glomerular and tubular function in autotransplanted dog kidneys preserved by hypothermic storage or machine perfusion. *Transplantation* 1986; 42: 453–458
8. Halloran P, Aprile M for the Ontario Renal Transplant Research Group. A prospective randomized trial of cold storage versus pulsatile perfusion for cadaveric kidney preservation. *Transplantation* 1987; 43: 827–832
9. Merion RM, Oh HK, Port FK, Toledo Pereyra LH, Turcotte JG. A prospective controlled trial of cold storage versus machine perfusion preservation in cadaveric renal transplantation. *Transplantation* 1990; 50: 230–233
10. Barber WH, Deierhoi MH, Phillips MG, Diethelm AG. Preservation by pulsatile perfusion improves early renal allograft function. *Transplant Proc* 1988; 20(5): 865–868
11. Alijiani MR, Cutler JA, DelValle CJ, Morres DN, Fawzy A. Single donor cold storage versus machine perfusion in cadaver kidney preservation. *Transplantation* 1985; 40: 659–661
12. Jaffers GJ, Banowsky LH. The absence of a deleterious effect of mechanical kidney preservation in the era of cyclosporine. *Transplantation* 1989; 47: 734–736
13. Tesi RJ, Elkhammas EA, Davies EA, Henry ML, Ferguson RM. Pulsatile kidney perfusion for preservation and evaluation: use of high-risk kidney donors to expand the donor pool. *Transplant Proc* 1993; 25: 3099–3100