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III. PATOLOGÍA CARDIOVASCULAR EN LA INSUFICIENCIA RENAL

Cardiovascular disease in chronic renal failure. Risk factors and prevention

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EPIDEMIOLOGY

After B. Scribner had introduced maintenance hemodialysis the naïve view had prevailed in many quarters that if one eliminated uremic toxins by hemodialysis, life expectancy would eventually approximate that seen in the general population. This naïve view was thoroughly dispelled when Lindner[1] reported 13 years later that more than 40% of the patients dialysed in Seattle had died, mostly from cardiovascular causes. As shown in figure 1, Raine subsequently documented that the risk of a dialysed

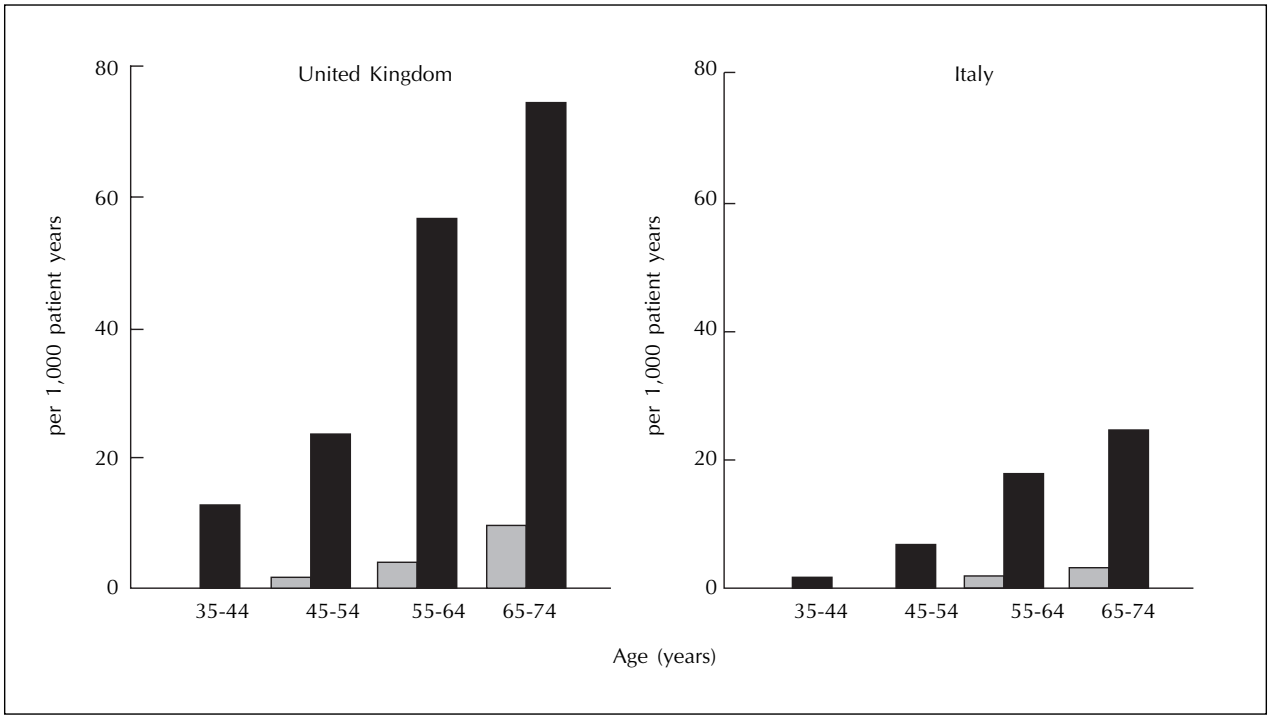

Fig. 1.—Comparison of death from ischaemic heart disease in the corresponding background population (grey columns) and in male dialyzed patients (black columns) in a country with high (UK) and low (Italy) cardiovascular mortality[2].

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patients to die from ischemic heart disease was higher by a factor of 15-20 compared to the background population[2] and this has recently been amply confirmed by Foley et al[2].

CAUSES OF CARDIOVASCULAR DEATH

In the past it had been assumed that ischemic events completely accounted for excess mortality. While ischemic heart disease is certainly extremely prevalent, the most frequent cause of death is sudden death, however[3], as shown in table 1. Whilst ischemic heart disease is an important cause of sudden death, it is most likely that other factors, particularly sympathetic overactivity and cardiac fibrosis (see below) play an important role. Furthermore, congestive heart failure, which carries a particularly poor prognosis[4] is very frequent in renal failure and is not fully explained by ischemic heart disease.

Table I. Adjusted cause specific death rates 1999-2001

Deaths per 100 pat. years	*(%)*	
Acute MI	19.9	(8.4%)
Cardiac arrest	51.9	(21.9%)
Cardiomyopathy	8.4	(3.6%)
Cardiac arrhythmia	11.2	(4.7%)
Heart valve disease	1.4	(0.6%)
Cerebrovascular	12.3	(4.7%)
Total	236 ppm	(100%)

After reference[3].

UNDERLYING PATHOPHYSIOLOGY

As postulated by Lindner[1], atherogenesis is undoubtedly accelerated in renal failure and, according to animal experiments, is seen in the very earliest stages of renal dysfunction, and even after uninephrectomy[5].

We have also postulated[6], however, that ischemic heart disease is so devastating in the renal patient because in addition the ischemia tolerance of the heart is reduced. We attribute this to several factors, including (i) left ventricular hypertrophy and the associated increase in oxygen demand, (ii) microvessel disease characterized by abnormalities of the vascular bed distal to the coronary conduit arteries, on the level of both arterioles and capillaries[6] as well as (iii) decreased hypoxia tolerance secondary to abnormal cardiac metabolism leading to instability of high energy nucleotides[7] and hyporesponsiveness to insulin[8]. Figure 2 shows that insulin-mediated glucose uptake is significantly decreased in the Langendorf heart preparation of uremic rats compared to controls[8]. The presence of ischemia intolerance is well illustrated by the

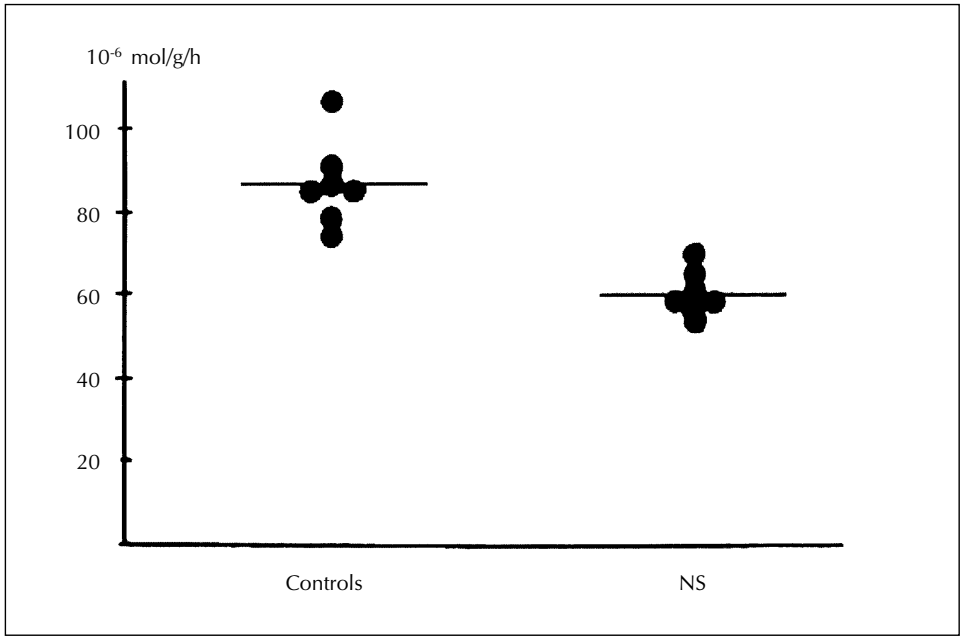

Fig. 2.—Insulin dependent glucose uptake in the isolated perfused Langendorf heart of uremic rats[8].

observation that coronary ligation causes larger zones of total necrosis in the heart of uremic as compared to control rats[9].

We wish to draw attention also to two further pathomechanisms which have been appreciated relatively late. Congestive heart failure carryies an excessively poor prognosis and may to a large extent be explained by cardiomyocyte drop-out presumably the result of cardiomyocyte apoptosis or necrosis. Amann found that the number of cardiomyocytes per left ventricle was reduced after subtotal nephrectomy and this defect was abrogated by the administration of ACE inhibitors[10].

Furthermore, it has been recognized that presumably through activation of intrarenal baroreceptors or chemoreceptors sympathetic activity is strongly stimulated in patients with endstage renal disease[11,12]. Klein et al.[13] could show that this abnormality was demonstrable in hypertensive patients with renal disease, even when glomerular filtration rate was not yet reduced. Not only is the sympathetic activity increased, but the response to sympathetic activation may be abnormal for two reasons. Autonomic polyneuropathy causes patchy cardiac denervation with presumed denervation suprasensitivity to catecholamines, thus aggravating the risk of arrhythmia. Second, the natural antagonist to catecholamines, nitric oxide (NO) is decreased because of inhibition of NO synthase by the circulating inhibitor ADMA and because of scavenging of NO as a result of interaction with reactive oxygen species. The high frequency of arrhythmia and sudden death in renal patients may to a large extent be explained by increased availability of, and reaction to, catecholamines.

RELATION OF RENAL DYSFUNCTION TO CARDIOVASCULAR RISK

It has only recently been recognized that even minor renal dysfunction strongly increases the risk of cardiovascular death[14]. After the initial observation in the Framingham study this has been well documented in the general population by Henry[15], in patients with hypertension by Ruilope[16], and in patients at high cardiovascular risk by Mann[17]. Henry et al. found that when GFR was lower by 5 ml/min. 1.73^2 the relative risk of cardiovascular death was higher by 26%[15].

If renal patients have an ischemic cardiac event in hospital mortality and post discharge mortality are dramatically increased[18] and the same is true after coronary intervention[19,20].

PREVENTION

Unfortunately there is no controlled prospective information on the effect of intervention. Nevertheless, based on observational studies and *a priori* reasoning, clinical common sense would suggest that the interventions listed in table 2 are sensible.

Blood pressure lowering

The initial fear that aggressive blood lowering would increase the risk of cardiac death as the result of a J-curve phenomenon was not confirmed in the MDRD trial. In a study on type 2 diabetic patients (ABCD trial) it had been shown that blood pressure lowering within the range of normotensive values significantly decreased stroke and tended to lower cardiovascular events[21].

RAS blockade

It is very likely that pharmacological blockade of the renin angiotensin system causes further blood pressure independent reduction of the cardiovascular risk[22]. The recent studies with angiotensin receptor blockers, i.e. the IDNT study[23] and the RENAAL studies[24] point to a tendency of lower cardiovascular events although both studies were not powered to prove this point.

Since ACE inhibitors have a beneficial effect on left ventricular hypertrophy, a known predictor of high cardiovascular risk, and reduce cardiac fibrosis as well as cardiomyocyte drop-out in experimental studies, routine RAS blockade does make sense. A recent retrospective study on dialysed patients even reported less cardiovascular events in dialysed patients on ACE inhibitors although this study certainly requires confirmation[25].

Table II. Cardiovascular prevention in renal patients

- Lowering of blood pressure
- Blockade of RAS
- â-blockade
- Statins
- EPO
- Aspirin
- Folate
- Vitamin E ?
- Vitamin C ?
- Control of phosphatemia,calcemia, PTH
- Avoidance of malnutrition

Betablockade

We postulated years ago[26] that uremic patients, particularly diabetic patients, should routinely receive betablockers. This was based on the observation that in a prospective study on dialysed type 2 diabetic patients only 4% of individuals dying of cardiac causes had received betablockers whilst 12% of those surviving had been on betablockers. The recent DOPPS study also shows significantly lower mortality in dialysed patients receiving betablockers for hypertension or ischemic heart disease. Improved survival or an improved ejection fraction has recently been demonstrated in dialysed patients who were treated with Carvedilol compared to patients receiving placebo[27]. Because of the above considerations betablockers are indicated even if there is no overt cardiac disease. This postulate is based on the consideration that these patients have both sympathetic overactivity and increased sympathetic reponsiveness. The argument holds even if patients are on ACE inhibitors, since, at least in non-renal patients the recent Capricon Study[28] documented that betablockers provided additional benefit even when patients had been on ACE inhibitors.

Lipid lowering agents

Because of the pathogenetic importance of dyslipidemia routine administration of statins appears to be clearly indicated, particularly since in 3 recent controlled prospective studies the sub-group of patients with impaired renal function was shown to derive benefit from administration of statins, i.e. in the ALERT[29] ASCOT[30] and CARE[31] studies. A retrospective analysis also showed an approximately 10% lower event rate in dialysis patients receiving statins[32]. The issue is currently under examination in the 4D study[33].

Anemia

It has only recently been recognized that anemia is a very strong survival factor in dialysed patients[34]. A. Levin further showed in pre-dialysis patients that if Hb concentration was lower by 0.5 g/dl the risk of an increase in LV mass was increased by 30%[35]. This finding is remarkable in view of the high predictive value of LVH for cardiovascular death.

Aspirin

There is no controlled evidence whether aspirin is equally effective in renal patients as it is in non-renal individuals, but there are good *a priori* reasons for routine administration.

Folate – Whether elevated

Homocystein concentrations are causally linked to cardiovascular death is uncertain, but since folate is both cheap and safe (at least if latent B_{12} deficiency is excluded) its use is certainly legitimate.

Antioxidants

Vitamin E is an interesting issue. Although all large studies in non-renal patients showed no benefit[36], a beneficial effect on cardiovascular events although not on cardiovascular death, was reported in a small study on renal patients[37] and an impressive beneficial effect of vitamin E administration on abnormal cardiovascular structure was documented in uremic animals[38]. Plausible reasons why vitamin E might be more effective in uremia could be very high oxidative stress and possibly also accumulation of biologically active vitamin E metabolites.

Malnutrition

Although malnutrition is not a conventional risk factor it has recently been shown to be a powerful risk predictor in dialysed patients and for this reason avoidance of malnutrition should be a matter of high priority[39].

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