II. ENFERMEDAD CARDIOVASCULAR EN HEMODIALISIS

Cardiac problems in dialysis patients

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Maintenance hemodialysis was introduced as a treatment of chronic renal failure. The common, perhaps somewhat naive, assumption was that removing uremic toxins would permit tha patient to live quasi undefinitely. Indeed, observations with patients who are now 30 years or more on dialysis, confirm that long survival is feasible, at least in principle. Nevertheless, in 1973 the Scribner group who had pioneered and introduced maintenance hemodialysis as a treatment modality reported the shocking observation that 30 of 60 patients on maintenance hemodialysis has died from cardiac causes[1]. This observation has been confirmed on numerous occasions. To explain this finding the speculation had been advanced that atherogenesis was selectively and specifically accelerated by uremia, but this appears unlikely. The most convincing evidence against is the observation that the rate of cardiac death does not progressively increase with time on dialysis as one would anticipate if atherogenesis were truely accelerated. If anything, the rate of cardiac death is highest in the first years of dialysis, presumably as a result of preexisting cardiac disease.

In order to appreciate the enormous magnitude of the cardiac risk of the dialysed patient we show this analysis of the late professor Raine[2]. Across the board cardiovascular mortality of the patient on renal replacement therapy is higher by a factor of 17-20, and this is true for males (with a higher baseline cardiac risk in the general population) and in females. If a patient has the double handicap of being British and requiring dialysis, again compared to the general population, the risk is higher by a factor of 20 (fig. 1).

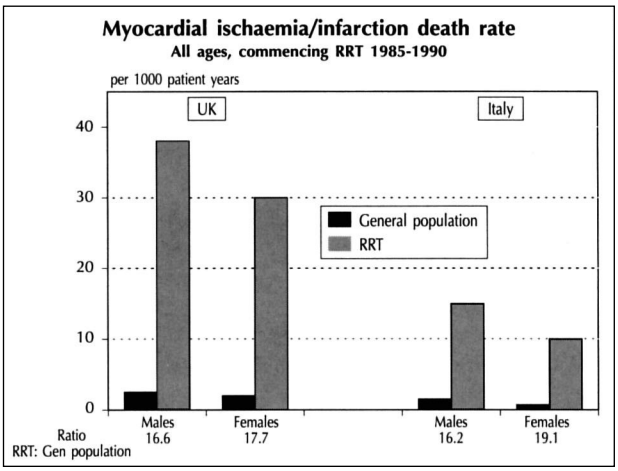

Fig. 1.—Comparison of death rates from myocardial ischemia and infarction in all male and female RRT patients and in the general population in Italy and the United Kingdom. Despite the diffe - rences in absolute mortality rates in the two countries, the ratio of increase in mortality in patients on RRT compared to the general population remains remarkable constant.

In order to provide an adequate basis of comparison, let us consider all cause mortality not cardiac mortality in the screenees of the MRFIT study. Total mortality was 11 per 1000 patient years.

Compare this with uremic patients in the United Kindgdom, commencing renal replacement therapy in the early eighties. Death from myocardial infarction alone was 20 per 1000 patient years (20-fold higher than total mortality in the MRFIT study!) and was even 3-fold higher than this if the patients happened to be diabetic.

The enormity of this risk is illustrated by the fact that of the placebo arm of the ISIS-2 trial, i.e. in survivors of a myocardial infarction, the group with the highest known cardiac risk, was 26/1000 patient years. So the cardiac risk of the patient on dialysis is comparable to that of survivors of myocardial infarction (table I).

I emphasize that only a proportion of cardiac death is the result of myocardial infarction. A number of studies showed that sudden cardiac death was

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Table I. Cardiovascular mortality in dialysed patients.

# MRFT screenee cohort 10 year follow-up (n = 347,978)		
hypertensive	diabetic	10/1000 pt years **total** mortality
	non-diabetic	3/1000 pt years
# ISIS-2 post myocardial infarction trial placebo group (n = 1241), 4 year follow-up		
		26/1000 pt years **MI** mortality
# UK endstage renal failure patients commencing renal replacement therapy 1981-1985 (n = 6742), 5 year follow up		
	diabetic	65/1000 pt years **MI** mortality
	non-diabetic	20/1000 pt years **MI** mortaliy

at least as frequent, if not more frequent, than classic myocardial infarction. What is it that puts the uremic patient at such enormous cardiac risk? We do not know the answer today, but whatever the answer is, it must be something which is quickly reversible. In a recent report of the Catalunya registry, two groups of elderly patients were compared. They had either remained on the waiting list and continued on dialysis or they were subjected to transplantation. Less than two years after transplantation, the incidence of various causes of cardiac disease, ischemic heart disease, cardiomyopathy or cardiac arrhythmia, had decreased by 50%. So whatever the cause of cardiac death it must be rapidly reversible[3].

The topic of cardiac death on dialysis is so large that we can cover only selected aspects. First we wish to emphasize some points relating to coronary death and then discuss non-coronary factors which might affect the tolerance of the heart to ischemia in the renal patient.

The frequency of coronary stenosis in the adult dialysis population, according to several studies using coronarography or autopsy, is 30-40%. Surprisingly, this is equivalent to what is found in the general population, particularly if one takes into consideration the highly atherogenic constellation of risk factors with hypertension and hyperlipidemia.

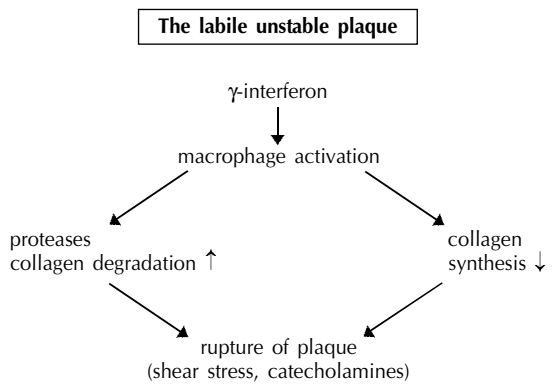
As recently reported by Enriques in the USA, the prevalence of coronary stenosis, assessed by routine coronarography in patients during preoperative evaluation of aortic insufficiency, did not change in the past decade, although the incidence of death from myocardial infarction in the general population decreased dramatically.

It appears as if the plaques had become more «benign». There is a surprisingly poor correlation between coronarographic evidence of coronary plaques on the one hand, and risk of myocardial infarction on the other land. This has led the concept of the labile unstable plaque[4]. After cell activation, schematically shown in table II as the result of gamma-interferon, activated macrophages disturb the delicate equilibrium between collagen synthesis (creating the protective fibrous cap) and collagenolytic breakdown of the fibrous cap. If the fibrous cap is dissolved as a result of diminished collagen synthesis and enhanced collagen degradation, it will rupture, release procoagulant factors and cause coronary thrombosis. Such rupture may be promoted by mechanical wall stress, for instance after release of catecholamines, a finding which would explain the high incidence of myocardial infarction in the morning hours or during emotional stress as documented by the recent observation of excess myocardial infarction during the Hanshin earthquake in Japan.

There is evidence to assume that plaques are more labile in the uremic patient. In an ongoing study we examined coronary lesions in uremic patients. We noted enormous intimal proliferation in uremic patients and could reproduce this finding in experimental animals. One striking feature also was extensive calcification of coronary plaques in the uremic patient, the combined consequence of hyperphosphatemia and hyperparathyroidism. In our view, this sequela of hyperphosphatemia is much more threatening to patient survival than the classical forms of extraosseous calcification.

We do now wish to go into any further detail, excepto to say that it is possible that we have to revise our simplicistic views on coronary atherosclerosis in the uremic patient. The question arises whether dialysis, although not accelerating formation of pla-

Table II.



ques (i.e. athrogenesis), may modify atherosclerotic plaques by making them more labile and thrombosis prone.

WHAT FACTORS CAN WE IDENTIFY WHICH ACCOUNT FOR NON-CORONARY CARDIAC DEATH?

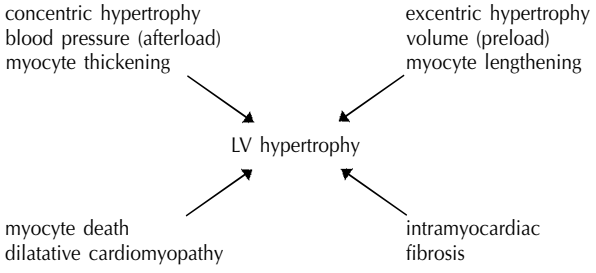
Recently, much attention has been attached to left ventricular hypertrophy. Table III shows that two factors account for left ventricular hypertrophy (i) elevated afterload, mainly through elevated blood pressure, which causes concentric hypertrophy as a result of thickening of myocytes and (ii) increased preload from hypervolemia causing excentric hypertrophy as a result of lengthening of myocytes. Both factors operate in renal failure. As a result one finds a variable mixture of concentric and excentric hypertrophy. This is accompanied by pathological intramyocardiac fibrosis which is not seen in physiological forms of hypertrophy, e.g. the athletes heart. The process may or may not lead to cardiomyocyte death resulting in dilative cardiomyopathy.

In essential hypertension, left ventricular hypertrophy is predictive of ventricular arrhythmia and cardiac death, independent of blood pressure and the same has been observed in dialysed patients [5].

Which factors have to be considered in the genesis of left ventricular hypertrophy? These include hypertension and fluid overload, as mentioned above, but in addition also anemia of renal failure and the hypercirculatory state resulting from an AV fistula.

Left ventricular hypertrophy may also result from accompanying diseases; in the dialysed patient one has to consider ischemic heart disease (resulting from compensatory overwork of non-affected LV segments) and acquired valvular disease (aortic stenosis resulting from hyperphosphatemia).

Table III.



That hypertension is not required for LVH to occur is documented by the observation of Hüting [6], who studied normotensive dialysis patients at a two years interval. The thickness of the interventricular septum increased significantly despite the absence of hypertension.

WHAT MAY BE THE CAUSES?

First of all it is obvious that normotension according to World Health Organisation may not be good enough for the renal patient. The evidence of the famous center in Tassin in France indicates that cardiovascular death rate is almost 6-fold higher if mean arterial pressure is above compared to below 99 mmHg. This dividing line would be equivalent to approximately 130/75 mmHg!

I do not wish to go through all these potential factors and draw your attention only to one neglected aspect that is diminished elasticity of central arteries. Stiffening of the aorta should increase the kinetic work of the heart, i.e. the expenditure of energy to accelerate blood during systole [7].

Fig. 2 (courtesy Dr. London) illustrates what diminished aortic elasticity implies for heart function in the renal patient. It shows schematically the left intraventricular pressure as well as the aortic pressure in a control subject and hemodialysis patient. In the uremic patient, peak systolic pressure is higher, causing increased kinetic work during ejection. While the heart has to perform more work, it also experiences an accelerated decrease of diastolic blood pressure as

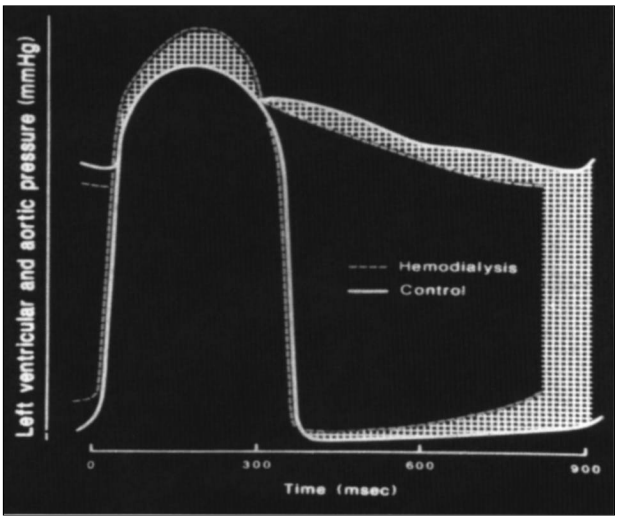


Fig. 2.—Schematic drawing of aortic pressure and left ventricular pressure in a hypothetical normal person and uremic patient respectively.
(Courtesy of Professor London [Paris].)

a result of diminished aortic elasticity. This must reduce coronary perfusion because diastolic flow occurs only during diastole. Coronary perfusion is even further restricted, because left ventricular end diastolic pressure is elevated in the renal patient because of impaired left ventricular compliance.

Let us consider some of the consequences of left ventricular hypertrophy and reduced left ventricular compliance.

In the presence of diminished compliance, left ventricular filling is more dependent on atrial filling pressure. If a patient is hypervolemic, there will be a disproportionate rise of left atrial pressure predisposing the patient to flash pulmonary edema. On the other hand, in the presence of hypovolemia (for instance during volume subtraction by ultrafiltration) there will be a disproportionate decrease of left atrial pressure and the patients' stroke wolume will decrease culminating in hypotension. A relation between left ventricular hypertrophy and risk of intradialytic hypotension was shown by Ruffmann[8]. The left ventricular mass/volume ratio was compared in patients with and without frequent intradialytic hypotension. The ratio was increased in the presence of frequent intradialytic hypotension, that is to say these patients had thick-walled LV ventricles with small lumina. That intradialytic hypotension may pose a hazard was shown in one of our prospective studies on 200 diabetic patients. Subjects who had more than two episodes of systolic hypotension below 80 mmHg had a 3-fold higher risk of cardiac deaht[9].

Without discussing details we add that apart from altered LV compliance, hypertrophic ventricles may have reduced coronary reserve (mind the patient with aortic stenosis who has angina pectoris despite patent coronary arteries). They are also more predisposed to ventricular arrhythmia.

THIS BRINGS US TO THE TOPIC OF REDUCED CORONARY RESERVE

Coronary perfusion is normally autoregulated, i.e. coronary blood flow is kept constant despite changes in coronary becomes pressure-dependent. The difference between basal flow and maximal flow perfusion pressure. If one vasodilates the coronaries, for instance by administering dipyridamol, the coronaries are maximally dilated and flow is designated coronary reserve. It is reduced in hemodialysis patients, partly because of coronary vasodilatation in response to anemia, but structural vascular abnormalities account for this defect as well. This comprises abnormalities of the capillary bed and of arteriolar vessels.

In the study depicted in table 3 we measured the length density of capillaries in the heart of uremic animals[10]. The length density is conceptually the length of all capillaries added one to the other per unit volume of the left ventricle. It is obvious that compared to controls, capillarisation is diminished in the left ventricle of uremic animals and this is true even when compared with rats with Goldblatt hypertension matched for left ventricular weight. The same is seen in the heart of uremic patients (unpublished studies). Consequently, some factors in uremia must prevent the capillary bed to increase in parallel with the augmented cardiomyocyte mass. In other words cardiomyocytes outgrow capillary supply. This must increase the average oxygen diffusion distance and expose the heart to the risk of critical hypoxia. This is of interest both with respect to pathogenesis of ischemia intolerance and with respect to its modification by antihypertensive treatment. In our studies, calcium channel blockers did not affect capillarisation, but defective capillarisation was almost normalized by ACE inhibitors and sympathicoplegic agents[11].

Let us now consider the arterioles of the myocardium[12]. In subtotally nephrectomized rats, the wall/lumen ratio of arterioles (as well as more sophisticated stereological indices of arteriolar wall mass) were significantly increased, 77 vs. 56 (as indicated in table IV). This was not the banal result of hypertension, since antihypertensive treatment with a diuretic and a vasodilator failed to normalize this ratio. Why is this of interest?

Table IV. Length density (LV) of capillaries in heart of uremic animals.

	controls (n = 7)	uremic (n = 8)	Goldblatt hypertension LV weight matched (n = 10)
LV (mm/mm^3)	3,364 ± 183	2,485 ± 264	3,155 ± 312

Cardiologists have known for a long time that some patients may have angina pectoris despite patent coronary arteries. These subjects have reduced coronary reserve as evaluated with dipyridamol. It has been documented that their intramyocardial arterioles are thickened. This may not necessarily increase basal vascular resistance, but will certainly impede flow reserve in response to vasodilatory signals, e.g. during ischemia.

To make matters worse, not only is coronary reserve diminished, but cardiac metabolism is also ab-

normal in a way which predictibly will reduce tolerance to ischemia. We had shown[13], that insulin-mediated glucose uptake is reduced in the isolated perfused Langendorf heart preparation (fig. 3). Why is this important? When the availability of oxygen is decreased, and when in parallel generation of ATP via mitochondrial oxydation is reduced, the heart must rely on ATP generation through cytoplasmic glycolysis. Compensatory glycolysis must become rate limited because of limited availability of substrate when insulin-mediated glucose uptake is diminished.

Second, the later professor Raine[14] showed that during low flow ischemia, energy-rich nucleotides, specifically ATP and ADP, are degraded and the irreversible endproducts inosine is released from the heart of uremic compared to control animals when studied by nuclear magnetic resonance spectroscopy. This was accompanied by increased cytosolic calcium. Consequently, a number of structural and metabolic factors conjure to render the heart more susceptible to ischemia (and by implication to cardiac death).

WHERE CAN WE INTERVENE?

First, a paramount task of the nephrologist is to avoid all risk factors of coronary disease. This includes the meticulous control of hypertension and treatment of hyperlipidemia which we did not touch upon. It also necessitates, however, elimination of additional risk factors, particularly smoking (mind that the half life of nicotine is prolonged in renal failure).

The evolution of the coronary plaque can be influenced. Lowering of lipids transforms plaques from unstable rupture-prone plaques into stable plaques - a clear rationale for lipid lowering in the renal patient with coronary disease.

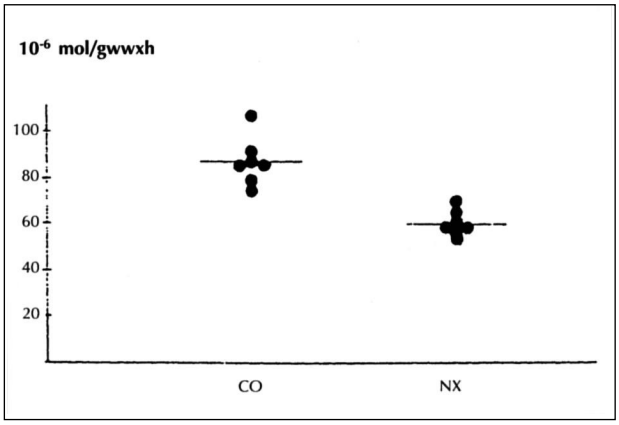


Fig. 3.—Comparison of insulin-dependent glucose uptake in the isolated perfused heart of rats with uremia.

It goes without saying that raising hematocrit will be beneficial, both by reducing the hypercirculatory state and by improving tissue oxygenation - we do not go into the current controversy about which hematocrit is optimal in this situation.

Left ventricular hypertrophy should be prevented, and if present reversed. There is now clear evidence from Canella[15] that ACE inhibitors are effective in this respect and to a lesser extent reversal of anemia by erythropoietin treatment.

The vascular abnormalities are responsive to sympathetic blockade and ACE inhibitors. Interestingly enough, vascular hypertrophy is dependent on the permissive effect of PTH[16] adding one more rationale for the control of hyperparathyroidism.

Our experimental studies (unpublished) suggest an important role of endothelin. Whether endothelin receptor antagonists will turn out to be effective, must be clarified by appropriate studies.

If patients happen to have ischemic heart disease. Hemodialysis is the worst that can happen to him, because it may cause tachycardia, positive inotropy and hypotension.

Reflex tachycardia during ultrafiltration shortens the diastole, i.e. the period of effective coronary perfusion - clearly unwanted.

Regular dialysate calcium concentrations increase inotropy - again clearly undesirable in the presence of ischemic heart disease. As a consequence, dialysate calcium concentration should be adjusted.

Table V. Wall thickening of intramyocardial arterioles in left ventricle of subtotally nephrectomized (NX) rats - unrelated to blood pressure.

	blood pressure [mmHg]	wall/lumen ratio [x 10^{-3}]
control	110 ± 13.3	56 ± 11
control + furosemide + hydralazine	99 ± 8.1	52 ± 6
NX	132 ± 20.7	77 ± 11
NX + furosemide + hydralazine	103 ± 13.0	66 ± 7

Finally, hypotension is absolutely deleterious as shown by our prospective study. In order to avoid this complication, less intradialytic weight gain should be aimed at and lower rates of volume substraction should be adopted. The first requires dietary sodium restriction to reduce thirst and reduce interdialytic weight gain. The latter necessitates longer more frequent dialysis sessions (eventually even four times per week). The importance of this is docu-

mented by recent results of the Japanese dialysis registry[17], where actuarial survival was clearly dependent on the duration of dialysis session (increasing with increasing duration) and clearly dependent upon interdialytic weight gain (and by implication rate of ultrafiltration).

Why are cardiac problems so important in the dialysis patient? Cardiac death is the most important cause of death in the dialysis patient. If we wish to improve survival in our dialysis population, resolving these cardiac issues will be the single most important measure to improve the currently still bleak prognosis of the dialysis patients under our care. These issues are the single most important challenge to todays nephrology!

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