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Cardiovascular disease in renal allograft recipients

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Over the past two decades, renal transplantation has become a safer procedure with an increase in one year patient survival from around 80 per cent in the late 1970s to just over 90 per cent in the late 1980s. However there is still a considerable mortality in the longer term with, in the UK, a survival rate in patients receiving transplants in the 1980s of 79 per cent at 5 years and only 63 per cent at 10 years[1]. Also a change has occured in the relative frenquency of the causes of death as illustrated by our own experience in Glasgow. Among our patients receiving renal allografts between 1968 and 1979, 37 per cent of deaths were due to infection and 21 per cent to cardiovascular disease. By contrast, among those receiving trasplants between 1984 and 1987, only 10% of deaths were due to infection while cardiovascular deaths had increased to 72% of the total. Thus in recent years cardiovascular disease has come to dominate the causes of death, certainly in the UK. This is due mainly to failure of cardiovascular deaths to decline in frequency while the other causes have become less common.

The main diseases which cause cardiovascular deaths are well known namely coronary artery atheroma leading to myocardial infarction, cardiac failure and arrhythmias, cerebral artery atheroma leading to cerebrovascular accidents and thirdly hypertension.

The effect of age on cardiovascular deaths is clearly shown in the 1991 European Dialysis and Transplant Association Registry Report[2]. Deaths with a functioning kidney at 5 years due to cardiovascular causes rose from one per cent in those aged from 15-24 years to 12 per cent in those aged over 65 years. However if one compares the risk of death from cardiovascular disease with the general population, the relative risk in patients on renal replacement therapy (RRT) is greater in younger than in older patients. In a study in Manchester the relative risk overall was 10 but was as high as 29.5 in patients less than 35 years old, falling to 6.9 in those aged over 65 years[3]. In addition to the effect of age, there are also well known effects of sex and country of residence. For example in the UK the mortality from myocardial ischaemia or infarction in men on RRT was shown to be 4 times higher then in Spain and in Norway it was 9 times higher then in Spain[2]. Finally in diabetics on RRT the already high risk of cardiovascular death associated with renal failure is even further increased, for example, by a factor of three to four in young men in the UK and to an even greater extent in young women[2].

A number of aetiological factors have been clearly shown to be associated with atheroma and most of these occur more commonly in renal transplant recipients than in the general population (table I). Serum triglyceride levels may fall following transplantation but serum cholesterol has been reported to remain high or even rise further[4]. Hypertension occurs in around 70 per cent of renal allograft recipients and glucose tolerance is adversely affected by steroids and other immunosuppressive drugs. Advanced glycosylation end-products (AGE) are thought to have a role in atheroma and we have found their tissue levels to be elevated in renal failure although there is a fall after transplantation[5]. However measurement of total serum cholesterol in the Glasgow renal allograft recipients has not shown any correlation with mortality in that there were no more deaths in patients with the highest levels than among those with lower levels.

Left ventricular hypertrophy (LVH) is common in patients being treated by dialysis and it has been shown to be an independent risk factor for survival in such patients[6]. However some of the causes of LVH in patients on dialysis programmes cease to be relevant following transplantation such as anemia, chronic fluid overload and in some patients, arterovenous fistulae. Also left ventricular mass has

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Table I. Factors predisposing to atheroma in chronic renal failure.

Hyperlipidaemia
Hypertension
Impaired glucose tolerance
Advanced glucosylation end-products (AGE) formation
Leucocyte activation
Obesity*
Smoking*

* Not linked to chronic renal failure but important factors in the general population.

been shown to regress after transplantation[7]. Thus we thought it worthwhile to examine the effect of left ventricular mass measured at the time of transplantation on subsequent patient survival.

Of the 228 patients who received a renal allograft between January 1988 and July 1990, 141 has an echocardiogram carried out immediately prior to the transplant. The recordings were coded and later analysed blindly by the operator. Left ventricular mass (LVM) was determined from Devereaux and Reichek's formula[8] and corrected for body surface area to give the LVM index (LVMI). The 141 patients were divided into three groups, alive (107) total died (34) and died from cardiovascular disease (21). The median follow up was 6.5 years.

The LVMI was increased prior to transplantation with a median value of 144 g/m^2 which compares with an upper limit of normal of 131-143g/m^2 for men and 100-102 g/m^2. This would lead to classification of 64-70 per cent of the men and 63-65 per cent of the women in this study as having LVH. In addition two other major left ventricular abnormalities were recognised, namely left ventricular dilatation and reduced systolic function. In our patients, the median end-diastolic volume was 133 ml compared with an upper limit of normal of 90 ml and this resulted in 83 per cent of our patients being classified as having left ventricular dilatation.

Echocardiographic assessments of LV mass and function were available for 27 of the 34 patients who died and 93 of the 107 who survived. LVMI was significantly higher, by about 30 g/m^2, in the patients who died in comparison with those still alive (Figure 1). Also when patients were stratified according to LVMI, there were twice as many deaths in the group with LVMI above the median. Thus our data confirm previous findings in dialysis populations. In addition they show that despite the presumed beneficial effects of transplantation on the left ventricle, brought about by correction of anaemia and fluid overload, the presence of increased LVMI at the time of transplantation has an adverse effect on life expectancy. Also our studies have shown that the ventricular chamber diameter, as measured by end systolic diameter (ESD) and end diastolic diameter (EDD) was a more significanty determinant of the likelihood of survival then the LVMI.

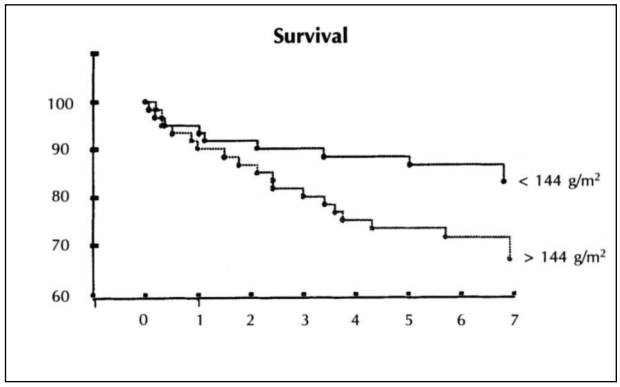

Fig. 1.—Per cent patient survival plotted against time in years in patients whose LMVI was greater than and less than 144 g/m^2.

Further studies are necessary in order to more accurately define the causes and relative importance of increased LV mass and ventricular chamber dilatation. The major determinants of LV mass in the general population are blood pressure and age. In our patients, we found no relationship between LV mass and age and only a weak one with blood pressure. Our investigations do not enable us to separate the effect of fluid balance and of primary cardiac disease on the ventricular chamber diameter ie ESD and EDD. The questions as to whether improved control of fluid balance and/or blood pressure in patients on haemodialysis will result in regression of LVH and normalisation of chamber diameters and whether in turn this improves life expectancy remain to be answered.

Although echocardiography is widely used, it requires experienced personnel for its operation and interpretation and this imposes a limit on the frequency of its use and its availability. by contrast the electrocardiogram (ECG) forms part of routine assessment prior to renal transplantation. As the prognosis significance of the ECG in this setting has not been examined, we have retrieved ECGs recorded immediately prior to transplantation of patients who

subsequently died. The ECGs belonging to patients who received their transplants between 1985 and 1995 were scored for LVH and other abnormalities. These patients have been matched for year of transplant, age and sex eith surviving patients.

The analysis was carried out for the entire group and then repeated excluding patients with diabetes mellitus. In this study there was no significant difference in prevalence of hypertension nor in the serum cholesterol or triglyceride levels between patients who died and those surviving. There was a trend towards more smokers in the deceased group and more with a history of myocardial infarction. By contrast, there was much more often a history of angina in those who subsequently died ($p < 0.0001$). However the most important findings were the presence more often of ECG changes of LVH ($p < 0.014$) or LVH and strain ($p < 0.0004$) in the deceased group in comparison with the survivor group. Patient survival at 8 years was 80 per cent in patients whose ECGs wer normal at the time of transplantation and this was double the mean survival in all the patients taken together who had abnormal ECGs (ie left bundle branch block, previous myocardial infarct, myocardial ischaemia, LVH and strain).

The main findings of our echocardiogram and ECG studies were that LV hypertrophy, increased LV chamber volume and the ECG changes of LV strain and myocardial ischaemia were all highly correlated with an increased likelihood of dying following renal transplantation. While I would not suggest that blood pressure and serum lipid levels are unimportant, they were not found to be predictive factors in the patients whom we followed up after transplantation.

As a sequel to our studies, it is important to determine if the increased cardiovascular risk we have demonstrated can be reversed. Three potentially useful initiatives worth pursuing in dialysis patients are better blood pressure control, maintaining a higher haemoglobin and avoiding fluid overload. The blood pressure target should probably be the middle of the normal range rather than around its upper limit, as is often the target at present. The goal of a higher haemoglobin than currently aimed at can be achieved by a combination of reducing dialyser blood loss, correcting occult iron deficiency with greater use of intravenous iron and thirdly giving higher erythropoietin doses. The last of these of course has a considerable financial implication and setting too high a haemoglobin target also may lead to an increase in thrombotic complications. Minimising fluid overload is straightforward in theory but difficult in practice. The most useful measure in furthering this aim is probably to extend the number of hours of dialysis per week to 20 or more rather than the usual current target of 12 to 15. However this measure also has financial implications and patient compliance may not always be possible.

Finally another mechanism which may be important is that of myocardial fibrosis. This may lead to arrhythmias and sudden death which are common in renal failure patients. It may also contribute to heart failure which in turn has, of course, a markedly adverse effect on patient survival.

In conclucion, increasd LV mass, dilatation of the left ventricle and myocardial ischaemia all predispose to premature death following renal transplantation. Greater effort is required in the attempt to prevent and/or reverse these pathological changes both before and after renal transplantation.

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