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Eberhard Ritz
Vedat Schwenger
Manfred Wiesel
Martin Zeier

Atherosclerotic complications after renal transplantation

E. Ritz (✉) · V. Schwenger · M. Zeier
Department Internal Medicine,
University of Heidelberg,
D-69115 Heidelberg, Germany

M. Wiesel
Department Urology,
University of Heidelberg,
Im Neuenheimer Feld 110,
D-69120 Heidelberg, Germany

Present address:
E. Ritz, Department Nephrology, University of Heidelberg, Bergheimer Straße 56a,
D-69115 Heidelberg, Germany,
Tel: + 49-6221-91120,
Fax: + 49-6221-162476

Abstract Death with functioning graft, the most frequent cause being cardiac death, continues to be the most frequent cause of long-term graft loss. The risk of cardiovascular death in the transplanted patient is lower than in patients with other modalities of renal replacement therapy, but continues to be substantially higher than in the general population. Amongst the factors predicting patient and graft survival are hypertension, dyslipidemia, smoking and possibly hyperhomocysteinemia. It is concluded that lowering of blood pressure to levels far lower than levels accepted in the past, more widespread administration of statines, cessation of smoking and possibly administration of folate should reduce cardiovascular mortality and possibly also influence chronic allograft vasculopathy.

Key words Atherosclerosis · Renal transplantation · Hypertension · Left ventricular hypertrophy · Hyperlipidemia · Statines · Hyperhomocysteinemia

The risk of cardiovascular death

According to Lindholm et al., the Scandinavian experience shows that between the second and third year after transplantation 41.4% of grafts are lost as a result of chronic rejection, but no less than 42% are lost because of death with a functioning graft [1]. This clearly illustratres that reduction of cardiovascular death would be a very efficient way to preserve grafts and improve graft outcome. The recent National Kidney Foundation Task Force on Cardiovascular Disease compared the frequency of coronary heart disease (CHD), and left ventricular hypertrophy (LVH) in the general population and in relation to various modalities of renal replacement therapy [2]. These complications are less frequent in transplanted patients (15% CHD, 50% LVH) compared to patients on hemodialysis (40% CHD, 75% LVH) or peritoneal dialysis (40% CHD, 75% LVH), but are still higher by a factor of two to three compared to the general population (5–12% CHD, 20% LVH) Myocardial infarction is the main cause of death in renal patients [3], but it is encouraging that the age-specific annual death rates have improved in recent decades for patients on renal replacement therapy [4].

Although mortality is higher amongst transplanted patients compared to the general population, transplantation clearly provides a survival advantage compared to other modalities of renal replacement therapy. This has been elegantly shown by Ojo et al. [5] who compared hemodialysed patients on the waiting list and patients receiving a graft. There is a transient period postoperatively when for obvious reasons mortality is higher after transplantation, but subsequently transplanted patients fare better than dialysed patients. The cardiovascular survival advantage is further illustrated by a study of the Catalunya registry [6] which compared the frequency of ischemic heart disease, cardiomyopathy and arrhythmia in hemodialysed patients on the transplant waiting list and in elderly transplanted patients, i.e. those above 60 years of age. Within months following transplantation, there was a dramatic decrease in the rate of all three morbid conditions. The frequency of

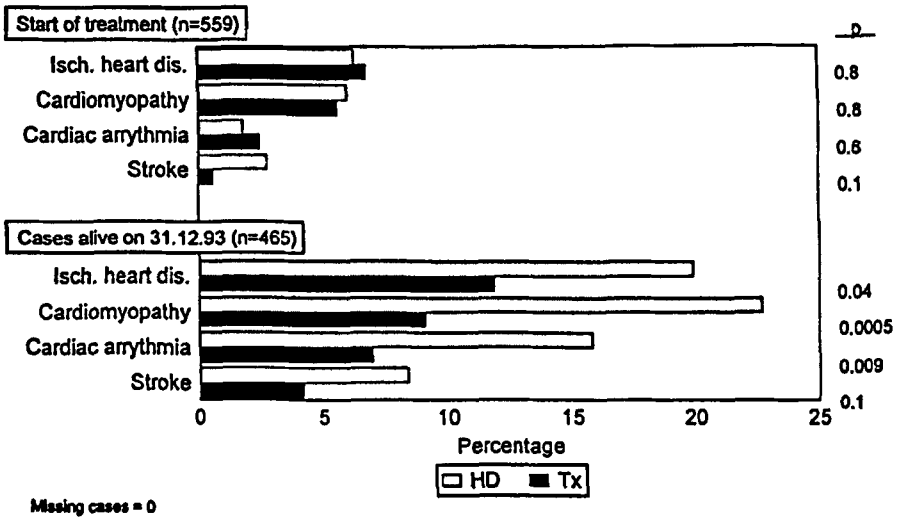

Fig. 1 Proportion of patients with cardiovascular comorbidity – comparison of elderly transplanted patients (*TX*) and hemodialysed patients (*HD*) on the waiting list (after reference 6)

cardiac problems had been similar in dialysed and transplanted patients at the time of operation, but was markedly less in the transplanted elderly patients during follow-up (Fig. 1). Actuarial 5-year survival was 86% after transplantation compared to 70% on hemodialysis – a 16% advantage in favor of transplantation.

Predictors of cardiac death in the transplanted patient

By multivariate analysis, Cosio et al. [7] have found that age, diabetes, smoking and length of time on dialysis are independent predictors of death after transplantation. The finding that time on dialysis is significant invites a comment. It has been found that very early in the evolution of renal disease there is an increase in cardiac risk factors. Stefanski et al. [8] have reported higher blood pressure values, albeit within the range of normotension, and left ventricular remodelling in normotensive patients with IgA glomerulonephritis even when inulin clearance is still normal. Also with a normal inulin clearance, patients with renal disease have pronounced insulin resistance [9] and higher Lp(a) levels [10]. It is obvious that the renal patient is exposed to a high cardiovascular risk profile from the very earliest stage of renal disease onward. A large proportion of patients enter renal replacement therapy with vascular damage, accumulated during the evolution of the renal disease. This provides a very strong argument for early management of the cardiovascular risk profile in the preuremic phase and justifies efforts to keep the time on the waiting list as short as possible, also from a cardiovascular point of view.

It comes as no surprise that cardiovascular abnormalities at the time of transplantation are potent independent predictors of death with a functioning graft. This is shown by the study of MacGregor et al. [11] who noted that at the time of transplantation echocardiographic parameters were significantly different between patients who remained alive after transplantation and those who die, most with a functioning graft (Table 1). This was true for left ventricular mass index, very striking for end systolic diameter (an index of disturbed systolic pumping function), end diastolic diameter and fractional shortening (an index of disturbed systolic function). It is of note that these indices improve as shown in a large prospective Canadian cohort study on individuals followed after successful renal transplantation [12]. In this relatively short-term study the rate of de novo ischemic heart disease was relatively low, 1 out of 102 patients. This is in striking contrast to the much higher rate reported by Kassiske et al. [13] who observed de novo CHD in 20% of patients alive with a functioning graft for 15 years. Although geographical

Table 1 Echocardiographic findings and survival in renal graft recipients (after reference 11). Data are medians (range) (*CVD* cardiovascular death, *LVMI* left ventricular mass index, *FS* fractional shortening, *EDD* end diastolic diameter, *ESD* end systolic diameter)

Parameter	All patients (n = 141)	n	Alive	n	Dead	n	CVD	n
LVMI (g/m^2)	144 (47–506)	120	134 (47–506)	93	167 (87–430)	27	177 (101–430)	17
FS	0.31 (0.05–0.54)	119	0.33 (0.09–0.54)	92	0.27 (0.05–0.45)	27	0.23 (0.05–0.45)	16
EDD (cm)	5.3 (3.0–7.5)	120	5.2 (3.1–7.5)	93	5.8 (3.0–7.3)	27	5.9 (4.4–7.5)	16
ESD (cm)	3.7 (2.1–7.1)	120	3.4 (2.1–6.5)	93	4.3 (2.7–7.1)	27	4.7 (2.9–7.1)	16

Table 2 Achieved clinic blood pressure in 90 long-term (> 2 years) renal graft recipients in the outpatient clinic, Heidelberg. Values are medians (range). There was no significant difference between genders. There were significant correlations between S-creatinine concentration and systolic blood pressure ($r = 0.23$, $P < 0.05$) and diastolic blood pressure ($r = 0.22$, $P < 0.05$). Antihypertensive agents: calcium channel blockers (77% of patients), diuretics (62%), betablockers (42%), ACE-inhibitors or AT-II-receptor-antagonists (13%)

Age (years)	48 (18–67)
Male/female	61/29
S-creatinine (mg/dl)	1.47 (0.83–8.1)
Systolic BP (mm/Hg)	135 (110–180)
Diastolic BP (mm/Hg)	80 (60–105)
Patients on antihypertensive agents	81/90
Number of antihypertensive classes	3 (1–7)

differences between the USA and Canada cannot be excluded, the main explanation is presumably the time factor, i.e. the duration of observation.

Potentially correctable cardiac risk factors

Hypertension

What medical authorities consider as normal blood pressure in the general population has progressively decreased with time, from the WHO definition of 140/90 mmHg to the recent Joint National Committee VI report of 130/85 mmHg [14] and the corresponding WHO-ISH statement [15]. The National Kidney Foundation [16] even recommends a target pressure of 125/75 mmHg–primarily to prevent progression. It is of interest that in one large controlled trial, the MDRD trial [17], such aggressive lowering of blood pressure was not associated with higher cardiovascular risk. This is important because one would have predicted otherwise if the concept of the J-curve [18] were valid, i.e. the notion that lowering diastolic pressure below 85 mmHg increases the risk of cardiac death. So while the cardiovascular benefit of aggressive lowering of blood pressure in the renal patient is currently not proven beyond doubt, at least it does not cause cardiovascular harm.

There are cogent arguments to consider blood pressure, particularly systolic blood pressure, as an important modifiable risk factor both for patient death and allograft failure [19]. It has been noted that there is a continuous increment in risk for graft survival, for patient survival and for functional graft survival as a function of increasing systolic, and somewhat less diastolic, pressures. There is a tendency for this to be true even for values within the range of normotension. Although obviously the graft is both the culprit and a victim of high blood pressure, there are some good arguments that blood pressure plays a causal role in graft failure; e.g. the relationship has been seen in recipients without rejection and normal serum creatinine concentration at the end of the first year after transplantation.

It is easy to justify the rigorous target blood pressure levels recommended by the JNC VI [14], but it is certainly difficult to achieve them. The failure to reach target blood pressure levels in patients with primary renal disease has been documented by us before [20] and the same is also true for renal graft recipients, as shown in Table 2 which shows an audit of 90 renal graft recipients followed for more than 2 years after transplantation in the Heidelberg outpatient clinic.

Mechanisms by which hypertension affects cardiac survival

There is no doubt that hypertension accelerates coronary heart disease. But the relationship between blood pressure and cardiac death is more complex. Lipkin et al. [21] have shown that ambulatory blood pressure (much more so than clinic blood pressure) is strikingly correlated with the degree of LVH and this correlation holds true even in the range of normotensive blood pressure values. It is therefore of interest that after successful transplantation left ventricular mass decreases significantly, but to a modest extent, as shown by Hernandez et al. [22] and other investigators. This observation is also of interest for another reason. Based on knock-out models in mice, it has been shown that calcineurin, i.e. NF-AT3, is important in the genesis of LVH [23]. Conversely administration of cyclosporin A interferes with the development of LVH in some models [24] but this is still controversial [25].

One novel aspect is the fact that not only mean arterial pressure, but even more so blood pressure amplitude, is predictive of cardiac death in renal patients [26]. A high blood pressure amplitude is a reflection of increased aortic impedance which is caused by increased aortic stiffness and diminished compliance. It is therefore of relevance that carotid artery elasticity is diminished in transplant recipients [27].

The role of dyslipidemia

The presence of dyslipoproteinemia in graft recipients has been known since the early days of renal transplantation [28]. Immunosuppressive medication plays an important role in its genesis, in the past steroids, today cyclosporin A or to some extent tacrolimus, and in the future sirolimus. Dyslipidemia is of course of considerable concern in view of the devastating risk of ischemic heart disease, and the influence of cholesterol concentrations on patient survival (Prof. Opelz, personnel communica-

tion), but possibly also because of its effect on chronic allograft dysfunction [29].

In a 15-year follow-up after transplantation, reported by Kassiske et al. [30], some of the independent predictors of ischemic heart disease were non-modifiable, e.g. age, diabetes and male gender, but some were potentially modifiable, particularly lipid concentrations and episodes of rejection.

Of great interest is Lp(a). Cressman et al. [31] showed that Lp(a) concentrations were an independent predictor of cardiovascular disease in uremic patients, but more recent work has shown that it is not the concentration, but the phenotype that is predictive of cardiac events [10]. There are several reports in small series, uncontrolled for phenotype, that Lp(a) concentrations decrease after renal transplantation [32], but Lp(a), although very interesting and important pathogenetically, is unfortunately not susceptible to intervention.

Of greater interest in this context are other lipoprotein classes, particularly LDL-cholesterol and total triglycerides. Wanner et al. have recently discussed the use of statines both to prevent cardiovascular disease and to prevent allograft failure [33]. The latter consideration is based on the observation of Kobashigawa et al. [34] of a dramatic reduction of vascular rejection in cardiac allograft graft recipients. This question has also been addressed in the ALERT study for renal graft recipients; the study evaluated the effect of the statine Lescol. The indications for administration of statines are discussed below.

A very interesting new aspect has been provided by the late Russel Ross [35], who drew attention to atherosclerosis as a microinflammatory state. In renal patients Zimmermann et al. [36] and others have found that indicators of inflammation, e.g. acute phase proteins (such as C-reactive protein, Lp(a), fibrinogen), endothelial cell glycoproteins, fibrinolysis inhibitors, and cytokines, particularly IL-1β, alpha TNF and IL-6, are predictors of cardiovascular death. One might speculate that the finding that rejection episodes are a predictor of cardiovascular death [30] is not only explained by the higher cumulative dose of steroids and higher blood pressure values, but also – as an alternative or complementary possibility – by promotion of atherogenesis via an inflammatory state. Whilst this hypothesis is not proven, it would certainly not hurt to administer low-dose aspirin to transplanted patients with this rationale in mind.

Smoking

There is no direct evidence that cessation of smoking brings benefit to the patient with a graft, but in a retrospective analysis, Cosio et al. noted that current smoking was a significant independent predictor of patient death [7].

Hyperhomocysteinemia

Hyperhomocysteinemia has recently been recognized as a significant risk factor for cardiovascular disease [37]. This is apparently also true for graft recipients. Massy et al. [38] have shown that elevated homocysteine concentrations are more frequent in transplanted patients with, as opposed to patients without, cardiovascular disease. It has been argued that in part the elevation of homocysteine concentrations is related to cyclosporin A therapy. There are both positive reports [39] and negative ones [40] and the final jury is certainly not yet in. Fodinger et al. [41] recently noted a strong influence of methylenetetrahydrofolate reductase polymorphism on homocysteine concentrations in transplant recipients.

Diabetes

Hyperglycemia and de novo diabetes are important risk factors for survival in transplanted patients [19]. Approximately 15–20% of graft recipients will ultimately develop diabetes. This is partly due to the influence of steroid treatment and more recently of FK-506. It is very likely, however, that these agents usually unmask an underlying genetic predisposition to type 2 diabetes, since the above proportion is exactly what is noted if patients survive to the age of 80 years – in other words further impairment of insulin sensitivity and, in the case of FK-506, also of insulin secretion, is a penalty one has to pay for effective immunosuppression.

Risk factor management in the transplanted patient

Pretransplant ischemic heart disease has been shown to be a strong independent predictor of cardiovascular death after transplantation [7, 13]. Consequently, cardiological evaluation of transplant candidates according to the guidelines of the American Society of Transplant Physicians is definitely a must to reduce cardiovascular risk [30].

As consultants we are repeatedly asked for dialysed patients with ischemic heart disease whether it is more sensible to have the patient transplanted first and then take care of cardiac problems, or the other way around. One-year survival of dialysed patients after myocardial infarction is a shocking 50% compared to only 10–15% in non-uremic subjects. This is a strong argument to have cardiac problems resolved before transplantation.

As to the modalities of prevention and intervention in established cardiac disease, no evidence from controlled trials is available for the management of a graft recipient – a sad reflection in this age of evidence-based medicine. Still, based on clinical common sense, a number of practical recommendations can be given.

1. *Blood pressure*: The observation of Opelz et al. [19] argues that one should aim for low blood pressure values. In patients with primary renal disease, lowering to 125/75 mmHg has been recommended [14] to attenuate progression. One can easily envisage that the inflamed vasculature of the graft should be similarly, if not more, susceptible to blood pressure values in the upper range of the norm. Based on experimental findings [42], the use of ACE inhibitors appears to be perfectly rational, but there is no clinical evidence for their superiority in transplanted patients and, incomprehensibly, there are still legal restrictions against their use in many European countries.
2. *Lipids*: In our view statines should be given to all graft recipients. This provocative view is based on the analogy to diabetes. Haffner et al. [43] have shown that the diabetic patient has a risk of cardiac death which is similar to that of a non-diabetic survivor of myocardial infarction. They argue that every diabetic patient should receive statines because these reduce the cardiac risk in primary prevention trials irrespective of baseline LDL cholesterol. One can extend the argument to the graft recipient who has also at least a threefold increased cardiac risk [2].
3. *Smoking*: Cessation of smoking would be desirable, but the success of advice to patients is limited. Of German heart transplant recipients, 20% resume smoking and in our experience no more than 15% of renal patients in our unit stop smoking despite strong and persuasive advice.

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