

Chronic rejection and hypertension: a chicken-and-egg problem

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Introduction

Elsewhere in this issue, Frei and co-workers report that the number of antihypertensive drugs needed to control blood pressure in 639 kidney allograft recipients was one of the most significant predictors of chronic progressive renal allograft dysfunction as defined by a 1/creatinine slope of >0.1 dl/mg/year [1]. Surprisingly this was not only true at 1 year after transplantation (where hypertension might be assumed to result from subclinical rejection or CsA toxicity), but also before transplantation. Antihypertensive therapy before transplantation was a much more important predictor than the degree of HLA matching and second only to the presence or absence of acute rejections. Although the study does not address the mechanisms by which pretransplant hypertension could impair long-term graft function, it raises the hypothesis that the recipient's cardiovascular risk profile has a profound effect on the transplanted kidney. This should prompt a reconsideration of non-immunological factors in chronic allograft rejection.

Morphology of chronic transplant rejection

The histological hallmarks of chronic rejection are fairly uniform in transplanted kidneys, livers, and hearts. They consist of arterial intimal thickening, for which the term 'fibroproliferative endarteritis' has been coined, and a persistent low-grade perivascular inflammatory infiltrate. Although these changes in some respects resemble 'simple' atherosclerosis, they may be differentiated by being both concentric (rather than eccentric) and generalized (rather than segmental). In the kidney these changes are accompanied by proliferative and sclerotic lesions of the glomeruli, by interstitial fibrosis, and by tubular atrophy.

Endothelial damage appears to be an early key event in both atherosclerosis and transplant vasculopathy, leading to attachment and penetration of mononuclear cells into the vascular intima whose proliferation may then be stimulated by a variety of growth factors (PDGF, TGF- β), vasoactive hormones (endothelin) and cytokines (IL-6). Once altered in this way, the vascular intima may become susceptible to the common atherogenic factors like hypertension and hyperlipidaemia. The increasing role of non-immunological factors after the initial insult is highlighted by attempts to

reverse the immunological component experimentally: retransplantation of an organ back to the original donor fails to reverse or stop the process if a critical time period has elapsed [2]. Consistent with this, fibroproliferative endarteritis is observed in long-term rat isografts as well as allografts, although it develops more rapidly in the latter [3].

Association of hypertension and progressive loss of renal graft function

Arterial hypertension, which occurs in some 50% of all renal transplant patients, is associated with decreased rates of graft survival and—consistent with the study of Frei et al.—with more rapid declines of GFR beyond the first year [4]. Commonly identified causes of post-transplant hypertension include pressor effects of the native kidneys, rejection, CsA therapy, and impaired GFR.

Since high blood pressure might be both the result and a causative factor of the destructive process, one would be grateful for a prospective study demonstrating the use of antihypertensive therapy. Unfortunately there is none, and the available retrospective evidence is equivocal. For example, in a study of 144 kidney transplant recipients, Cheigh and co-workers found no difference in graft survival between patients with controlled versus uncontrolled hypertension [5], although hypertension *per se* significantly impaired 10-year graft survival. In contrast, a study of 135 patients with grafts functioning at 1 year found that hypertensive patients did significantly better if their blood pressure was medically controlled [6].

Mechanisms by which hypertension may mediate graft loss

Beyond the 'atherogenic' effect on arteries and arterioles, hypertension may cause glomerular damage, if the systemic level of blood pressure is transmitted to the glomerulus. Grafts undergoing chronic rejection usually carry the stigmata of the hypertrophy→glomerulosclerosis pathway [7] as established by the studies of Brenner and others. Brenner recently advanced the concept that transplants are doomed to failure if the number of transplanted nephrons fails to match the recipient's requirements, resulting in hyperfiltration at the price of an increased glomerular pressure [8]. In the view established by Arthur Guyton, an insufficient number of nephrons would shift the pressure–natriuresis curve to the right, and hyperten-

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sion would develop because salt balance may only be achieved at increased blood pressure.

A mere 50% reduction of renal mass does not appear sufficient to initiate the vicious circle of hyperfiltration in humans, since humans uninephrectomized in adulthood consistently do well for long periods of time. In contrast, a single transplanted kidney may have an insufficient number of nephrons, if its mass is further diminished by rejection or CsA toxicity, or if there is a size mismatch with the recipient. Terasaki and co-workers have suggested that many graft failures labelled as 'rejection' may actually be 'hyperfiltration failures'. In the large UNOS registry, the following five situations are both associated with decreased graft survival and are likely to go along with hyperfiltration [9]: (1) transplantation of kidneys from small donors (ages 4–6) into adults; (2) transplantation into recipients > 100 kg; (3) transplantation of kidneys from females into males; (4) kidneys undergoing rejection episodes; and (5) cadaver kidneys in general relative to living donor kidneys.

Other non-immunological mechanisms in chronic graft rejection

Serum cholesterol appears to be an independent risk factor for transplant coronary vasculopathy in heart-transplant recipients [10], and elevated levels of LDL cholesterol were found to have a significant negative effect on 4-year kidney graft survival in 98 Finnish transplant recipients [11]. Interventional studies in kidney transplants are not available, but recent, preliminary data in heart-transplant recipients suggest that lowering serum cholesterol by pravastatin is able to decrease transplant coronary disease [12]. Among other common 'atherogenic' factors, smoking has not been found to be associated with an increased risk of chronic graft failure. The situation is similar with obesity: although a recipient weight > 100 kg was associated with an impaired 1- and 3-year graft survival in the UNOS registry, the difference did not appear to increase beyond the first year as one would expect if chronic rejection were favoured by obesity [9], and other authors found that obesity did not constitute a major risk for 3-year survival.

Pre-transplant hypertension and graft outcome

Although mysterious at first glance, there are several possibilities as to how pre-transplant hypertension might impair graft prognosis. First there is a close correlation of pre-transplant with post-transplant hypertension such that the same factors which render antihypertensive treatment difficult prior to transplantation (such as obesity, poor compliance, high NaCl intake, pressor effects of the native kidneys) are expected to operate after transplantation as well. Second, pre-transplant hypertensive patients may have adapted to a higher blood pressure for a long time and

their hypertension may therefore be harder to control after transplantation. Third, pre-transplant hypertension may be associated with a general propensity for atherosclerosis and hypercholesterolaemia and thus represent a risk indicator for the time after transplantation.

Consequences for patient management

As outlined, accumulating data suggest that hypertension and hypercholesterolaemia adversely affect the long-term fate of the transplanted kidney, but conclusive evidence for a protective effect of lowering blood pressure and cholesterol on chronic graft rejection is missing. The puzzling finding by Frei *et al.* that pre-transplantation hypertension is somehow connected with long-term graft function may lead one to suspect a negative effect of the native kidneys and to consider their removal. Predicting the success of this manoeuvre has, however, been exceedingly difficult and the morbidity not trivial. With today's antihypertensive drugs it should be possible to reach an acceptable level of blood pressure control in virtually every renal transplant patient. The ideal level, however, is entirely speculative. The similarity of chronic graft rejection with non-immunological progression of renal failure suggests that simple 'normalization' of pressure may not be enough and that 120/80 may be better than 140/90 [13]. To diminish glomerular hypertension and hyperfiltration, a decrease of GFR may be unavoidable, and medications currently promoted for their 'kidney sparing' effects may prove to be non-protective for that very reason.

Normalization of blood pressure and lipids has become standard medical management and is undertaken for reasons other than the prevention of chronic graft failure. We do, however, need studies which tell us what level of blood pressure we should target and which antihypertensive drugs are suitable. Meanwhile it may be wise to treat our patients' hypertension as aggressively after transplantation as we do before.

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Editor's note

Please see also the Original Article by U. Frei (pp. 1206–1211 in this issue).

When dialysis becomes worse than death

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Dialysis has become a readily accessible form of life-sustaining treatment. The criteria for accepting patients into chronic programmes have become less restrictive and today disabled patients, elderly patients, and patients with accompanying diseases are admitted for renal replacement therapy. In fact the continuous increase in the number of dialysis patients is explained by, amongst other factors, increasing acceptance of patients with poor prognosis [1,2]. Recent analyses of the causes of death in patients on dialysis revealed that, after cardiac events and infectious disease, withdrawal from dialysis is the third most common cause of death in the United States [3]. It is possible that withdrawal might become even more common in the future, as the number of disabled patients taken on chronic dialysis increases progressively.

The decision of a mentally competent patient to discontinue dialysis is now generally accepted in the US and the right of a patient to refuse life-prolonging treatment has clearly been established [4]. The American Medical Association has defined specific guidelines for physicians concerning the ethical and legal aspects of withdrawing life-sustaining treatments [5]; life-sustaining treatment is defined as any treatment useful to prolong life without reversing the underlying medical condition.

Physicians are obliged to promote the dignity and the autonomy of dying patients. The principle of patient autonomy implies that physicians must respect the decision to refuse life-sustaining treatment of a competent patient. The obligation to offer specific treatment for a specific disease therefore does not include an obligation to impose or to continue treatment on an 'unwilling' patient who has the freedom

to make his choice in accordance with his own values [6,7]. The physician is obliged only to offer treatment to relieve distressing symptoms, respecting the principles of 'non-maleficence' and of 'beneficence' for the patients [5].

I wish to argue that the crucial question facing physicians is whether or not 'to permit' patients to discontinue dialysis; it is essential that nephrologists have well-defined guidelines to review appropriately with the patient all circumstances and problems that might have led to the decision to discontinue medical care, because the patient feels it is no longer beneficial; the aim should be to modify the patient's decision. Evaluation and discussion between patient and nephrologist should include a complete review of the clinical circumstances, e.g. sources of pain, non-medical approaches to reduce suffering, poverty, loneliness, and loss of social role, prospects of transplantation, psychiatric treatment of depression etc. [8]. In fact, it is an illusion to think that patients do not suffer in the process of withdrawing from treatment and dying [9]. Nevertheless, patients become increasingly concerned that the dying process is needlessly protracted by biomedical technology, involving poor quality of life, intolerable pain, and loss of human dignity.

Prominent reasons given by patients for their decision to discontinue chronic dialysis treatment are dissatisfaction with life style, advancing age, with serious medical problems, physical impairment, neurological disability, severe pain, financial consequences of treatment, etc.

There has been a change in the 'culture' of dying. Until the recent past, sick people were treated at home, and usually patients also died at home. Today, however, the vast majority of deaths occur in medical institutions, laying the burden of ethical and legal responsibilities on the shoulders of physicians. In the

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