Editorial Comments

HLA-derived peptides as novel immunosuppressives

A. M. Krensky\textsuperscript{1} and C. Clayberger\textsuperscript{2}

Departments of \textsuperscript{1}Pediatrics and \textsuperscript{2}Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA, USA

Introduction

A basic understanding of the cellular and molecular mechanisms of organ transplant rejection may provide new insights into the mechanism of action of existing drugs and lay the foundation for the development of novel approaches to immunotherapy. We have focused on the T lymphocyte as a mediator of transplant rejection. T cells recognize foreign HLA on the graft and orchestrate various effector arms involved in both humoral and cellular immunity [1]. We designed synthetic peptides corresponding to structural regions of HLA molecules and used them to modulate the immune response. Over the past decade the use of such peptides has progressed from the bench to the bedside [2]. This report will briefly summarize this progress.

The role of HLA in the alloresponse

The human leukocyte-associated (HLA) antigens encoded in the major histocompatibility complex (MHC) on chromosome 6 in man subserve numerous functions in the immune response, but they were first identified as molecules that direct and restrict transplant rejection [3]. Studies of the structure of HLA class I (Figure 1) and definition of the structure and function of the T cell receptor provided new insights into the mechanism of HLA recognition, T cell activation, and differentiation, and the events leading to acute and subacute transplant rejection [1]. Non-self HLA molecules are recognized by T cell receptors by both ‘direct’ and ‘indirect’ pathways. In the direct pathway, whole foreign HLA is recognized, while in the indirect pathway, non-self HLA peptides are recognized in the context of self HLA (Figure 2).

HLA class-I-derived peptides

In 1985 we reasoned that linear sequences of HLA molecules may be important in the interaction between HLA molecules and T lymphocytes and set out to make synthetic peptides corresponding to these sequences as potential therapeutic reagents [4,5]. We first showed that peptides corresponding to specific HLA sequences could block cytotoxic T lymphocytes (CTL) in an allele-specific manner. Synthetic peptides corresponding to residues 98–113 of HLA-A2 specifically inhibited cytolysis directed at HLA–A2, but not other HLA types [4]. We proceeded to define a series of synthetic peptides corresponding to linear sequences of HLA molecules that blocked a variety of assays both \textit{in vitro} and \textit{in vivo} [5–7]. The most interesting of these peptides corresponded to the z1 alpha helix of HLA class I molecules (Figure 1). A subgroup of these peptides, corresponding to residues 60–84 of HLA-Bw4\textsubscript{4a}, inhibited cytotoxicity between all donor-recipient pairs \textit{in vitro}. Furthermore these human sequences induced immunological tolerance in animal models of transplantation (Figure 3) [8]. Based upon these studies, SangStat Medical Corporation, Menlo Park, CA, USA, licensed the peptide technology and developed it under the brandname ‘Allotrap\textsuperscript{®}’. In collaboration with Jean-Paul Souliillou and colleagues, SangStat showed that the Allotrap\textsuperscript{®} peptide was non-toxic in phase I clinical trials and embarked upon phase II trials in France. Recent results from this phase II trials in France. Recent results from this group show that the peptides inhibit natural killing (a surrogate marker for CTL and cell-mediated immune responses) \textit{in vivo} in patients who have received otherwise standard therapy for renal transplantation [9]. The mechanism of action of these peptides is still unclear. Of interest, however, the functional peptides, like the immunosuppressive drug deoxyspergualin, bind to members of the heat shock protein 70 family of chaperones [7]. In addition, these peptides correspond to regions of HLA class I molecules recognized by natural killer inhibitory receptors, KIR. These receptors send inhibitory signals into natural killer cells when they recognize HLA molecules on target cells [10].

HLA class-II-derived peptides

Gallon \textit{et al.} found that synthetic peptides corresponding to linear sequences corresponding to polymorphic
regions of mHC class II molecules had similar inhibitory effects both in vitro and in vivo [11]. They interpreted their findings in the context of competition for target antigens in ‘indirect allorecognition’. Recently we described a sequence corresponding to a relatively monomorphic region of an HLA class II molecule that inhibits T cell proliferation by blocking cell-cycle progression. This peptide, derived from the α1 α-helix of HLA-DQ 03011, inhibits proliferation of human peripheral blood lymphocytes, purified T cells, and cytolysis by CTL in an allele non-specific, dose-responsive manner. Proliferation to interleukin-2 (IL-2) was blocked, but signalling through the IL-2 receptor was intact. S6 kinase activity, downstream of the IL-2 receptor, is inhibited. Like rapamycin [12], this peptide inhibits cdk2 kinase activity by blocking degradation of the p27 cell cycle inhibitor. However, unlike rapamycin, the DQ peptide is unable to inhibit yeast cell growth. Thus a peptide from the same region of an HLA class II molecule as previously described...
Fig. 3. Survival of rat heterotopic heart allografts. LEW donor hearts were transplanted into the abdomen of ACI recipients and palpated daily. Rejection coincides with a loss of heart beat. Either (a) intravenous injection or (b) gavage of synthetic peptide B7 (corresponding to residues 75–87 of HLA-B7), with a 5-day course of oral cyclosporin, resulted in long-term graft survival. (Reprinted with permission from Krensky AM, Clayberger C. The induction of tolerance to alloantigens using HLA-based synthetic peptides. *Curr Opin Immunol* 1994; 6: 791–796.)

Summary and conclusions

Over the past decade the use of synthetic peptides corresponding to linear sequences of HLA molecules has progressed from a concept to a reality. These peptides are currently being evaluated in clinical trials. In animal models these peptides, given over 1 week with cyclosporin alone, induced long-term immunological tolerance (Figure 3). They may similarly induce tolerance in humans. The next major hurdle for such tolerogenic drugs, however, is to prove efficacy in clinical circumstances. Many of the drugs used to treat transplant patients today (steroids, cyclosporin, azathioprine, mycophenolate mofetil) may actually inhibit the 'active' processes of induction and maintenance of
immunological tolerance. Demonstration that new drugs induce tolerance will require efficacy studies in other immune-mediated diseases in which monotherapy is feasible (such as psoriasis), before further advances can be made in the induction of transplant tolerance. In addition, rapid assays of rejection must be developed in order to reverse tolerance induction failures without graft damage or loss. Lastly, it will require heroic physicians, surgeons, and patients to make immunological tolerance a reproducible clinical reality.

References

Blood pressure measurement and standards in children

W. Rascher
Zentrum für Kinderheilkunde, Justus-Liebig-Universität Giessen, Germany

Arterial hypertension is a well-recognized manifestation of various forms of renal disease also in children. Normal blood pressure standards have been satisfactorily defined in the paediatric age group, but the use of ambulatory blood pressure monitoring has introduced new problems.

How should blood pressure be measured in children?

The largest cuff which can be comfortably applied should be used, and its inflatable part (the bladder) should cover at least two-thirds of the circumference of the upper arm. In addition to the standard adult cuff with a bladder width of 12–14 cm, a bladder 8 cm wide should be used for small children. The lower edge of the cuff should not touch the stethoscope when this covers the cubital artery. If necessary, an even smaller cuff size of 5–6 cm can be used. The child should be sitting relaxed and comfortable. There is a general agreement that the appearance of the first Korotkoff sound should be used as a criterion for systolic blood pressure measurement. However, there is some discrepancy whether complete disappearance (phase 5) or muffling (phase 4) should be used as an indication of diastolic pressure. Whereas the Report of the Second Task Force on Blood Pressure Control in Children [1] recommends phase 4 in children and phase 5 in adolescents older than 13, the Recommendations for Management of Hypertension in Children and Adolescents [2] state that, in general, phase 5 should be used to indicate diastolic blood pressure in children and adolescents. If the value of phase 5 is close to 0, the measurement should be repeated; if the second measurement gives a similar value phase 4 should be used. In epidemiological studies, the difference obtained using the two phases to indicate diastolic pressure is only a few mmHg.

Measurement of systolic arterial blood pressure with Doppler ultrasound or mean arterial blood pressure with oscillometric devices are particularly valuable methods for the detection of arterial hypertension in neonates and small infants. Oscillometry is widely accepted in hospitals and by an algorithm both systolic...
and diastolic pressure are calculated from measured mean arterial pressure in a sufficiently accurate manner. In very-low-birth-weight neonates larger cuffs are more appropriate, but hypotension cannot adequately be detected in these infants. Normative oscillometric blood pressure values have been reported in very-low-birth-weight infants [3] and during the first 5 years of life [4]. Recent technological advances have enabled non-invasive repetitive blood pressure determinations over 24 h in subjects performing their normal activities. This new technique of ambulatory blood pressure monitoring has been introduced as a valuable method for the evaluation of arterial hypertension in adults as well as in children and adolescents [5]. In the paediatric age group nearly exclusively oscillometric ambulatory blood pressure monitors are in use. Whereas blood pressure can be measured accurately in mildly active or inactive children, no reliable measurements are obtained during exercise and vigorous physical activity [6]. Systolic and diastolic blood pressure follow a typical circadian rhythm, values being 15–25% lower at night than during the day.

What blood pressure is normal in children?

A number of epidemiological studies have established normal blood pressure values in different populations. Labarthe [7] reviewed 88 epidemiological reports on blood pressure in children from 30 countries: a consistent increase in both systolic and diastolic blood pressure with age was observed in almost all surveys. A marked increase in average blood pressure with age in childhood and adolescence may be one aspect of normal growth and development. Distribution and percentiles of general populations provide references for blood pressure in growing children: there is a progressive rise of casual blood pressure of approximately 1.5 mmHg systolic and 0.7 mmHg diastolic per year of age.

Combined data from several studies as references for casual blood pressure has been published from studies performed in the United States [1] and in Europe [8]. The United States data included one European study, the Brompton study of more than 7000 children aged from 4 days to 5 years [9]. Although the Task Force stresses the importance of making several blood pressure recordings in any individual child before drawing conclusions about the blood pressure, only the first blood pressure readings made in the 70000 subjects were used to prepare its standards, because in one of the nine studies just one blood pressure measurement per subject was available. In an attempt to incorporate the important contribution of body size into the analysis, the Task Force has added the 90th percentile of height and weight for normal children at the bottom of the charts. The European percentile charts have related casual blood pressure to height rather than to age. Recently, tables for blood pressure in children were published taken into account both age and height [10]. However, these Tables are rather difficult to handle in daily practice.

New information from ambulatory blood pressure measurements in children

Recently, reference values for ambulatory blood pressure monitoring of children and adolescents have been reported. A working group in Germany has reported normative reference values in 1141 children and adolescents that allows calculation of percentiles [11]. Compared to reference values obtained from casual blood pressure measurements [1,8] mean systolic daytime ambulatory blood pressure rose only moderately by height, from 112 to 124 mmHg in boys and from 111 to 120 mmHg in girls, whereas mean diastolic daytime blood pressure was 72–74 mmHg, irrespective of height or sex. Small children had systolic as well as diastolic daytime ambulatory blood pressure means significantly above normal casual blood pressure at rest, whereas this effect was less pronounced in taller adolescents. The reason for this discrepancy cannot be explained on a biological basis (e.g. higher level of physical activity throughout the day in younger children). Particularly, lack of rise in diastolic blood pressure during maturation does not correspond to the findings of casual measurements in a variety of epidemiological studies. Methodological difficulties (e.g. algorithm constructed for adults) might explain this phenomenon. There was a large decrease of blood pressure during the night by more than 20% of daytime pressure.

The diagnosis of hypertension in children

Criteria for the diagnosis of hypertension in adults are not applicable to children. A value of 140/90 mmHg for casual blood pressure and 135/85 mmHg for daytime ambulatory blood pressure is generally accepted as the upper limit of normal blood pressure in adults, and this might also be true for adolescents. Since a linear relationship exists between height and blood pressure and between log weight and blood pressure, a major blood pressure determinant in childhood is body size. Therefore it has been recommended that blood pressure levels in the growing child should be related to height.

Uncertainties exist with regard to normal blood pressure range, and there is no agreement on the exact definition of hypertension at different ages. The most helpful criterion for the definition of hypertension in children is the persistence of blood pressure above the 95th percentile. With repeated measurements not 5% (95th percentile), but even less (about 1%) of the children show chronic high blood pressure. When ambulatory blood pressure values with oscillometric devices are the basis to diagnose arterial hypertension, separate reference values should be used [11] (Table 1).
Intradialytic renal haemodynamics—potential consequences for the management of the patient with acute renal failure

M. Manns, M. H. Sigler and B. P. Teehan

Division of Nephrology, Lankenau Hospital, Wynnewood, PA, USA

Introduction

Hypotension is one of the major complications of haemodialysis. A symptomatic reduction in blood pressure occurs in approximately 20–50% of all acute dialysis treatments and results in interruption of the treatment in about 5–10% of cases. Several procedure-related and patient-related factors contribute to haemodynamic instability during dialysis. Among the procedure related factors are ultrafiltration-induced hypovolaemia, leading to a decrease in venous return and cardiac output, the rapid reduction in plasma osmolality, which causes extracellular water to move into cells and slow plasma refilling time [1]. Some studies suggest that a haemodynamic instability during traditional intermittent haemodialysis may have adverse effects on the course and recovery of acute renal failure (ARF). Less haemodynamic instability during slow continuous therapies could protect the kidney from further damage and might result in enhanced recovery.

Evidence for continuing tubular necrosis in acute renal failure

Conger suggests that repeated episodes of hypotension during dialysis may exacerbate renal injury and delay recovery from ARF [2]. Renal biopsies obtained 3–4 weeks after the initial insult from patients who suffered combat injuries with prolonged renal shutdown uniformly revealed areas of fresh tubular necrosis. All

## References

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## Note added in proof

US authorities have recently revised their guidelines and recommended the fifth Korotko/DC2 sounds to define diastolic hypertension in children [12].

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<tr>
<th>Height (cm)</th>
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Correspondence and offprint requests to: Miles H Sigler, Division of Nephrology, Lankenau Hospital, Wynnewood, PA 19096, USA.
patients had required daily or alternate day haemodialysis, and many dialysis treatments were complicated by transient blood pressure reduction to mean values as low as 70–90 mmHg, despite an overall stable clinical condition. The temporary decline of the blood pressure, which was within the autoregulatory range of the healthy kidney, seemed to be the only explanation for the presence of these new ischaemic lesions. Slez compared renal biopsies in 50 patients with persistent acute renal failure with biopsies from seven patients who had recently recovered from ARF [3]. The biopsies were taken 3–4 weeks after the onset of renal failure, at a time when regeneration of the damaged tubular epithelium should have been completed. Morphological analysis of the biopsies showed necrosis of the tubular epithelial cells and loss of the PAS-positive brush border in the proximal tubules, which were significantly more severe in the ARF group than in the recovery group. Both of these histological changes could contribute to renal function failure in ARF by permitting passive backflow of tubular filtrate and by causing decreased tubular reabsorption of sodium, resulting in stimulation of renin release and afferent arteriolar vasoconstriction [3]. Tubular casts seemed to play no role in the maintenance of renal failure. The data suggests that necrosis of tubular epithelial cells is a continuing process, not necessarily limited to the original lesion, and contributing to, if not causing, continued renal failure and prolonged ATN. These observations may be explained by the results of the animal experiments, described below.

**The post-ischaemic kidney in acute renal failure**

Animal experiments designed to evaluate possible relationships between alterations in renal haemodynamics and ongoing damage of the surviving or recovering nephrons showed an impaired ability to autoregulate renal blood flow in post-ischaemic ARF. Haemorrhagic reduction in renal perfusion pressure within the autoregulatory range was associated with paradoxical vasoconstriction (rather than vasodilation), leading to a substantial decrease in renal blood flow, further reduction in creatinine clearance and histological evidence of recurrent ischemic injury [4]. It was shown that the post-ischaemic kidney exhibits an increased sensitivity to renal nerve stimulation with exaggerated catecholamine release from nerve endings [5]. Furthermore, the ability to autoregulate renal blood flow was significantly improved after renal denervation [4]. In addition, the vasodilatory capacity of the post-ischaemic renal vessels seemed to be diminished, due to decreased or lost endothelium derived relaxing factor activity [6]. These results suggest that hypotensive episodes during intermittent haemodialysis may result in decreased renal perfusion pressure in the post-ischaemic kidney. If autoregulation of the post-ischaemic kidney is impaired, reduced renal perfusion pressure might induce paradoxical vasoconstriction with severely diminished renal blood flow and recurrent ischemic injury.

**Does renal replacement therapy affect the residual renal function in acute renal failure?**

We have studied the effects of intermittent haemodialysis (IHD) and continuous haemodialysis (CVVHD) on the residual kidney function in critically ill patients with acute renal failure [7]. The data has been published only in abstract form. Twenty-seven patients were treated with intermittent haemodialysis and 16 patients with continuous haemodialysis using polysulphone membranes in each group. Creatinine clearance, urea clearance, urine volume, and fractional excretion rate for sodium were measured for 3 h before dialysis, during dialysis and for 3 h after intermittent haemodialysis. The same parameters were determined for 3 h before, 0–3 h and 4–6 h during continuous haemodialysis. Virtually all renal function parameters changed significantly during and after intermittent haemodialysis, indicating an acute worsening of residual kidney function. Creatinine clearance, which represents an estimation of the glomerular filtration rate (GFR), declined significantly intra- and postdialysis, when compared to predialysis (Table 1). However, as GFR falls, enhanced tubular creatinine secretion leads to an up to twofold overestimation of GFR by the creatinine clearance. The variability of tubular urea reabsorption, which depends on the degree of sodium and water reabsorption, causes urea clearance to underestimate GFR by 30–50%. The mean of creatinine clearance and urea clearance, which may be a closer estimation of true glomerular filtration rate in patients with moderate to advanced renal insufficiency [8], was also substantially lower during and after dialysis compared to predialysis. However, if serum creatinine falls during dialysis below the saturation limit of the secretory mechanism, changes in creatinine clearance after dialysis may not necessarily reflect changes in GFR. In this case, the declining serum creatinine during dialysis would cause decreased tubular creatinine secretion, which in turn would falsely suggest a decreased GFR. Two studies investigated the effects of dialysis on creatinine secretion in chronic renal failure and the importance of creatinine clearance as an estimate of GFR in ARF. The first study showed an increased creatinine secretion

| Table 1. Effects of dialysis on residual renal function in acute and chronic renal failure |
|---------------------------------|--------|--------|--------|
|                                 | Creatinine clearance (ml/min) | Inulin clearance (ml/min) | Urine volume (ml/min) | FeNa (%) |
| Manns [7], ARF, CVVHD           | −7%    | −10%   | −12%   |
| Manns [7], ARF, IHD             | −25%   | −50%   | −46%   |
| Yeh [11], CRF, IHD only only UF | +5%    | −21%   | −43%   |
| Schück [9], CRF, IHD            | −4%    | −25%   | −30%   |
|                                 | −3%    | −35%   |        |
from 1.09 to 2.01 μmol/min 12 h after dialysis [9]. The authors propose the hypothesis that dialysis eliminates substances which inhibit tubular creatinine secretion. The second study reports a good correlation between creatinine clearance and inulin clearance in ARF \((r = 0.93)\) [14]. We believe therefore that the observed significant decline in creatinine clearance and urea clearance during and following intermittent haemodialysis suggests a marked decrease of the glomerular filtration rate.

There are several explanations for these observations. First, the MAP fell during IHD by 7% from a baseline of 84 mmHg. The correlation between the percentage decrease in creatinine clearance and the fall in MAP during dialysis \((r = 0.72, P < 0.001)\) provides evidence that renal hypoperfusion during and following dialysis might aggravate renal damage. Secondly, dialysis removes urea from the blood, which in turn reduces the urinary osmotic drive [10]. The decrease in urine output after dialysis in chronic renal failure is the result of reduced solute load with enhanced tubular reabsorption (Table 1) [11,12]. In our study of ARF the decrease in BUN during dialysis did not correlate with the fall in urine output or the fall in creatinine clearance. This makes it unlikely that reduced urinary osmotic drive during and after dialysis played a significant role in the observed changes [13]. This is in agreement with the results from Rahman and Conger, which demonstrate that the residual GRF is the primary determinant of the urine flow rate in ARF [14].

In comparison with the observed changes during intermittent haemodialysis, renal function parameters such as creatinine clearance, urine volume, and fractional excretion of sodium were significantly less affected during continuous haemodialysis (Table 1) [7]. Haemodynamic instability did not occur during CVVHD despite significantly lower baseline blood pressure before initiation of continuous haemodialysis. This improved haemodynamic stability during CVVHD might be the explanation for the better preservation of the residual kidney function. It also makes it less likely that, despite the use of biocompatible membranes in both groups, blood–membrane interactions such as activation of the humoral pathways and the cellular blood elements might have influenced renal function [15,16].

**Conclusion**

Renal hypoperfusion during intermittent haemodialysis might delay tubular regeneration in postischaemic ARF. Continuous forms of renal replacement therapy have several advantages in the setting of critically ill patients with acute renal failure [17,18]. Improved haemodynamic stability during continuous haemodialysis protects the kidney from further damage and might result in enhanced recovery. However, in our study [7] dialysis efficiency was substantially less during the first 6 h of CVVHD in comparison to IHD and further comparisons using comparable dialysis prescriptions in regard to urea clearance, solute removal and volume removal are necessary to confirm this advantage. Further research should also focus on the question of whether dialysis-induced hypoperfusion is limited to the kidney or whether it also affects other organ systems adversely. Our study was not designed to investigate possible differences between both treatment modalities in terms of mortality. The fact that CVVHD is associated with less change in residual renal function does not necessarily translate into improved morbidity or mortality.

**References**

Renal replacement therapy in the elderly: an old problem with young solutions

Nuahd Ismail
Division of Nephrology, Vanderbilt University School of Medicine, Nashville, TN 37232–2372, USA

Therapy of end-stage renal disease (ESRD) in the elderly is characterized by tremendous challenges. It also raises ethical and socioeconomic concerns: ethical issues because an expensive treatment is being offered to a population with limited life-expectancy, and socioeconomic because of the progressive increase in the proportion of elderly requiring ESRD therapy worldwide [1]. According to the US Renal Data System (RDS), 1995 Annual Data Report, the median age at incidence of ESRD has reached 62–63 years in the US, Japan, Germany, France and Italy [2]. Indeed, geriatric ESRD will be an important topic for 21st Century physicians to face. In the U.S., it is projected that 60% of the ESRD population will be over 65 years in the year 2000.

Factors to be considered in offering renal replacement therapy to elderly patients with ESRD

When making decisions about initiating, withholding, or terminating dialysis in the elderly or the appropriateness of offering renal transplantation to these individuals, several important points must be considered: (1) The elderly are a ‘heterogeneous’ group of persons united by ‘chronologic’, but not necessarily ‘biologic’, age (physiologic, psychologic, or social functioning). The latter (biologic age) has a variable expression depending on the pace of ageing as well as the impact of comorbid pathologic conditions whose number and severity increases with age. (2) When analysing results of renal replacement therapy (RRT) in the elderly, health care professionals must recognize the importance of not only ‘absolute’ survival time of these individuals, but also the ‘quality’ of that survival. Stated otherwise, the goals of RRT in the elderly is to add ‘life to years’, not simply ‘years to life’. Furthermore, while there might be little disagreement on the definition of quality of life, the yardstick for its measurement has not been straightforward. (3) When renal transplantation is being considered for the elderly, a dilemma exists if it is ‘fair’ to waste an invaluable resource (the cadaver kidney) to an elderly individual with a limited life-expectancy, i.e. send a functioning graft to the grave with the elderly.

Survival of the elderly on dialysis

Despite complex comorbid and psychosocial conditions, survival and the quality of life in the elderly patient on haemodialysis (HD) is frequently acceptable. The 5-year patient survival presently ranges between 20–40% [3]. Nevertheless, multiple studies have drawn different conclusions based upon the period of evaluation, type of patient, and study design. An early study [4] of 157 patients with a mean age of 75 years and multiple comorbidities at initiation of dialysis (17.2% of patients had diabetes, 35% had coronary disease, 10% had cerebrovascular disease, 18% had chronic obstructive pulmonary disease, and 22% peripheral vascular disease) found 3- and 5-year survival rates of 47% and 22%, respectively. Despite these comorbidities, most of the patients were doing well, had social contacts (90%), spent time outdoors (86%) and ranked high on Karnovsky scale (73% of patients with scale >80%). In addition, 40% perceived their health to be better than 70-year old subjects, while only 25% regarded their health as worse. An acceptable subjective quality of life and degree of rehabilitation have also been noted in other reports [4–8]. In the Battelle Human Affairs Research Center Study [8] of 859 dialysis and transplant patients, 70% of the elderly dialysis patients (comprising 16% of the total numbers of the elderly dialysis) fell in the top four categories of overall functional status using the Karnovsky index. It has been proposed that the regular visit to the dialysis unit and mixing with younger patients may act as a beneficial social stimulus in elderly patients [6]. However, the importance of this social effect is brought into question by the observation in one study that those elderly subjects treated by home HD had the highest quality of life, as assessed by life satisfaction, well-being index, and psychological effect [9].

Factors impacting on quality of life

Two more recent studies painted a much grimmer picture of the life of elderly dialysis patients [10,11], especially when ESRD is caused by diabetes. It is important, however, to appreciate the flaws in the design of these studies. These include basing the data on recollection in one study, not realizing the full benefits of erythropoietin, and not addressing dialysis adequacy. In addition, the conclusions may not apply to patients who do not live in the inner city. These studies, however, demonstrate the impact that poverty, illiteracy, and other urban troubles can have on the likelihood of rehabilitation. Therefore, negative results such as these should not provide ammunition for those who wish to institute age-based rationing of HD, but
rather, among other things, to examine the critical issue of rehabilitation and most importantly early implementation of measures that might improve functional status whenever it is significantly impaired.

A recent study suggested that racial differences may affect the outcome of elderly dialysis patients [12]. Black elderly patients were found to have higher survival rates (57 vs 38% at 3 years) and a better quality of life than white patients. The following factors may have contributed to these differences: (1) blacks spent more time on dialysis per week than whites, (2) whites had more dialysis-accelerated atherosclerosis, cardiovascular morbidity, and other comorbid conditions at 3 years and (3) blacks may be more likely to die of competing risks before reaching kidney failure; as a result, those who survive to chronic dialysis may constitute a ‘hardier group’.

In the aggregate, therefore, prolonged survival in the elderly on HD is feasible. Furthermore, the elderly can adapt to a complicated treatment regimen and activities, and may be more compliant than younger patients [13]. However, malnutrition and the potential for under dialysis, as well as depression and withdrawal from dialysis are serious complications in the elderly dialysis patient [14].

Dialysis technique and the elderly

The new synthetic membranes and the full benefits of erythropoietin hopefully will decrease the incidence of these complications in the elderly dialysis patient. Most importantly, delivery of ‘adequate’ dose of dialysis (KT/V > 1.4) is critical to the elderly. Five- and 10-year survival rates of 69% and 64%, respectively, were achieved in patients older than 64 years in one of the longest studies of high dialysis doses (KT/V = 1.67) reported from France by Laurent et al. [15].

Similarly, the outcome of chronic peritoneal dialysis (CPD) in the elderly is also acceptable, with 5-year survival rates of 20–30% [3,16–19]. CPD is thus an alternate dialysis modality for the elderly and may confer some advantages such as absence for vascular access and the promotion of independence and a sense of self-worth. Also the judicious use of CPD in nursing homes, the use of home helpers, and the development of Adult Health Care Centers may enable physicians to offer this modality to more elderly patients. Although many comparisons have been made of mortality between HD and CAPD for the ESRD population as a whole, only few specific studies have addressed the elderly subgroup. Overall, in terms of outcome, there is little evidence to suggest that one modality is superior for the elderly ESRD patients [20]. At least in the long-term, technique survival appears to be greater in HD-treated patients. Two recent epidemiological studies from the US suggest that HD may be associated with less mortality in the elderly diabetic (in the USRDS case-mix severity study, RR of death was 1.25 for elderly diabetic on CAPD compared to HD) [21,22]. All of the available studies comparing morbidity and mortality are limited, however, by small sample size or the possibility of selection bias among CAPD patients.

Transplantation in the elderly—an under utilized opportunity?

Over the last decade, the efficacy and safety of renal transplantation in the elderly has been demonstrated in several published reports [22–26]. One-year patient survival now ranges between 80–90% and 5-year patient survival for cadaveric renal transplantation (CRT) has increased to 70%. ‘Functional’ graft survival has increased in parallel, averaging 80% at one year and 55–60% at 5 years. The increasing success of organ transplantation in the elderly, coupled with a chronic persistent shortage in cadaver donors has created an ethical dilemma for physicians regarding the allocation of a scarce resource (the cadaver kidney) to the elderly with limited-life expectancy.

Ageing is accompanied by senescence of the immune system [27]. The T-lymphocyte population undergoes major alterations with age resulting in a decline in cell-mediated cytotoxicity. T-cells of elderly do not recognize self-MHC. These changes lead to down regulation of the T-cell activation cascade, with less rejection episodes to organ transplantation. On the other hand, these changes also lead to a decline in cell-mediated immunity against viral, bacterial, and fungal infections. B-cell function is unimpaired in the elderly; however, reduced antibody response to foreign antigens declines because of impaired CD4+ helper function. This trade-off (decreased rejection and increased vulnerability to infection) necessitates modification of immunosuppressive therapy in the elderly.

Patient death with a functioning allograft accounts for the majority of graft loss in older transplant patients [22–26]. In several studies, older patients had a graft loss rate of nearly 50% as a consequence of death compared to a rate of 15% in younger patients. Since graft loss in the elderly is related primarily to patient death (and not immunologic graft-loss), and the two main causes of mortality following transplantation are cardiovascular disease and infection, it follows that comprehensive preoperative evaluation of elderly patients is imperative to improve patient and thus graft survival. Similarly, the goal of immunosuppression protocols in the elderly should be to reduce the risk of infection without causing rejection and consequent high-dose immunosuppression, infection, and graft loss. Since the elderly have a degree of immune incompetence and decreased hepatic enzyme activity (especially the P450 enzyme system), they require less aggressive immunotherapy.

Recent data from USRDS and from UNOS have revealed that recipients of older kidneys (donor age 56–65) on average have lower graft survivals and lower GFR’s, without affecting patient survival [28]. These decrements in graft function are magnified at a donor age above 60, and are reflected more in long-term...
survival (after 3 years) than in 1-year graft survival. The increased (but acceptable) risk of graft loss permit the conclusion that the donor pool should be expanded to routinely include kidneys up to donor age of 60 years, that routine peri-harvest renal core biopsies should be used to evaluate the integrity of renal anatomy in donors between 60–65 years, and that older kidneys might be harvested for particular use in older recipients when 20–30 year graft survival are not as important as in younger recipients. This age matching of donor and recipient is gaining support both as a fair and a physiologically fair process [28, 29]. Further support for age matching comes from a recent report that kidneys from older donors survived for longer in older patients than in younger patients [30].

Finally, living-related transplantation may confer some benefit (compared to CRT) in graft survival; its major limitation, however, remains the finding of a suitable living donor [31].

Conclusions

In summary, (1) elderly patients should not be denied either transplantation or dialysis on the basis of age per se. Irrespective of age, they should be offered dialysis if there is no contraindication (senile dementia, metastatic cancer, and advanced liver disease). Dialysis however should not be used merely to prolong the dying-process, nor should dialysis facilitate a longer life of a quality considered unacceptable. When there is doubt about chances of recovery from a severe underlying illness, a ‘trial’ of dialysis may be offered to an elderly patient (several weeks and perhaps few months). Withdrawal of dialysis later would be preferable to withholding it. A ‘biologically’ well maintained elderly <70 years old (and possibly <75) free of recent or metastatic malignancy, active infection, severe extrarenal disease (cardiac, pulmonary, hepatic) or mental or psychiatric illnesses should be considered for renal transplantation (Figure 1). (2) Expanding the donor pool to include older donors (56–65) is a suitable strategy if judiciously applied (excluding such kidneys when serum creatinine is >1.8–2.0 mg/dl). Such older kidneys may be appropriately matched to older recipients. (3) Elderly patients should receive extensive information about ESRD therapy modalities. They should be able to select the modality that maximizes their quality of life (including psychosocial adaptation). They should also be considered for rehabilitation programs.

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Vascular access thrombosis—what are the possibilities of intervention?

M. Mysliwiec
Department of Nephrology and Internal Medicine, Medical University, Bialystok, Poland

Introduction

Vascular access represents the Achilles heel in today’s haemodialysis treatment. The preferred form is a primary arteriovenous fistula that has longest survival time and a low complication rate. However, in some patients the vessels are unsuitable for primary arteriovenous fistula creation. Currently, the more common form of vascular access in such patients is polytetrafluoroethylene (PTFE) graft.

Vascular access and haemostasis

Thrombosis is a leading cause of any vascular access failure, and usually results from stenotic lesions caused by progressive neointimal hyperplasia in the venous outflow system, probably caused by a turbulent flow, and leading to increased shear stress stimulation of local growth factors or their release from platelets and leukocytes [1,2]. Under shear stress in the HD fistula, platelets are directly activated, adhere to the vessel wall, and release their constituents, which recruit other platelets and form aggregates which promote development of thrombosis. Glycoproteins GP Ib, GP IIb/IIIa and extracellular Ca$^{2+}$ are absolute necessities for this process. Intact endothelial cells exposed to a high shear force produce various vasodilatory, platelet inhibitory (NO, PGI$_2$) and fibrinolytic (t-PA) mediators that mitigate the activation of platelets and preserve blood fluidity. However, when the endothelial cells (EC) are injured they are not able to oppose shear-stress-induced platelet aggregation, thus promoting platelet thrombus formation. Needle puncture leading to endothelial damage may also play a role.
An obstruction to venous outflow typically occurs within 5–6 cm of the arteriovenous anastomosis in a fistula and within 2–3 cm of the venous anastomosis of the graft. It is more proximal in 15–20% of cases. Hypertrophied venous valves and sites of intimal trauma from old temporary catheters in central veins may lead to their stenoses and disturb outflow of blood from the distal access.

**Can one identify the patient at high risk?**

There is a higher risk of blood access failure in patients with severe vascular endothelial injury, a useful marker of which is a high plasma thrombomodulin [3]. Predisposing factors are diabetes mellitus, hypotension, hypoalbuminaemia, anticardiolipin antibodies, hyperhomocysteinaemia, and increased serum levels of lipoprotein (a).

In a 2-year, cross-sectional, prospective pilot study in 30 non-diabetic haemodialysis patients with primary arteriovenous fistula in 11 (37%), a progressive stenosis of the venous circuit, complicated by thrombosis in three of them was found [1]. Compared with 19 patients without fistula dysfunction, they had higher serum levels of monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6), two cytokines that regulate the proliferation of vascular smooth muscle cells (VSMC). In addition they had hyperinsulinaemia, hyperlipidaemia (high triglycerides and the ratio for cholesterol/HDL cholesterol), and increased plasma levels of tissue plasminogen activator inhibitor (PAI-1) and factor VII.

**Is there a role for serotonin and cytokines?**

Serotonin (5HT) released from dense granules of platelets may also stimulate thickening of the blood vessel wall in several ways. By amplifying the release of other aggregatory agents, 5HT facilitates ongoing platelet aggregation and thus the growth of factors, in particular platelet-derived growth factor (PDGF). Even at low concentrations serotonin stimulates directly the mitogenesis of vascular smooth muscle cells in culture. In vascular smooth muscle cells it significantly potentiates the mitogenesis induced by PDGF. The 5HT2 receptor antagonist, ketanserin, besides lowering the arterial blood pressure, exerts a significant antiproliferative effects on vascular smooth muscle cells [4]. Growth of vascular smooth muscle cells is also promoted by thrombin and angiotensin II.

In haemodialysis patients the increased concentration of IL-1 beta and TNF alpha may induce endothelial cells to increase prothrombotic activities including production of IL-6 and PAI-1, expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [5]. The enhanced circulating levels of VCAM-1 and ICAM-1 probably are the result of activation of endothelial cells and increased leukocyte/endothelial cells interactions.

**Is there evidence for genetic predisposition?**

Resistance to activated protein C (APC) caused by a single point mutation in the factor V gene (factor V Leiden) was recently identified as a thrombophilic defect which is strongly associated with deep venous thrombosis and recurrent idiopathic thromboembolism. However, a heterozygous carrier status for factor V Leiden does not appear to be a risk factor for vascular access thrombosis in haemodialysis patients, possibly due to a high functional APC activity, which is very close to or within the normal range [6]. It cannot, however, be excluded that a homozygous factor V mutation represents an increased risk for shunt thrombosis.

**Thrombosis of vascular access—non-surgical options**

A treatment of access dysfunction requires a combined medical, surgical, and radiologic approach. The primary non-surgical therapy is angioplasty. Thrombolytic therapy may be tried as well. Valji et al. [7] modified thrombolysis by a placement of two specially designed catheters with multiple side holes into the thrombus, oriented in opposite directions. Urokinase in a dose of 250 000–500 000 units is then injected in small pulses as the catheters are advanced and withdrawn. A 98% success rate of that ‘pulsed-spray pharmacomechanical thrombolysis’ was reported. Newer techniques are intravascular stents and directional atherectomy [8].

**The role of anticoagulants and platelet inhibitors**

Anticoagulants and antiplatelet agents may be used in patients with recurrent graft thrombosis but always after ruling out an anatomic cause for thrombosis. An attempt to identification of all contributing factors to thrombosis including hypercoagulable state should be pursued.

There are no prospective, randomized studies to demonstrate a beneficial effect of vitamin K antagonists in preventing graft thrombosis. Of many antiplatelet drugs acetylsalicylic acid (ASA) has been most studied. It induces irreversible inactivation of platelet cyclooxygenase. Although, none of the trials achieved acceptable statistical significance, most of the studies involving aspirin, alone or combined with dipyridamol, displayed trends toward prevention of fistula thrombosis [9]. Therefore if there are no contraindications ASA may be used for prevention of both threatened and recurrent fistula thrombosis. Enteric-coated ASA in a dose of 150–325 mg once a day after breakfast may be recommended.

ASA does not inhibit ADP, thrombin, serotonin, and PAF-induced platelet aggregation. These mediators are generated and accumulate at sites of endothelial injury and vascular stenoses and they may be responsible for reduction in blood flow in these
patients. In addition cyclo-oxygenase inhibition may shift arachidonate metabolism toward non-prostaglandin metabolites (e.g. lipo-oxygenases) that might promote intimal hyperplasia.

Ticlopidine inhibits aggregation induced by ADP, collagen and thrombin by preventing exposure of fibrinogen receptors GP IIb/IIa on the platelet membrane, which is a common pathway of the platelet aggregation. It acts only in vivo and requires several days of oral administration before achieving its full antiplatelet effect. Probably its platelet-bound metabolites are active as antiplatelet agents. Additionally, ticlopidine stimulates early fibrinolysis possibly due to an inhibition of the release of PAI-1 from platelets [10]. Ticlopidine has theoretical advantage over ASA as it does not inhibit PGI$_2$ synthesis in the vascular endothelium and is an antioxidant. Its ability to inhibit fibrinogen binding to platelets supports its use in all patients, but especially in those who cannot take or have failed to respond to ASA. It appears to be a useful agent for prevention of fistula thrombosis. Ticlopidine may be combined with ASA [11].

The frequency of unwanted effects of ticlopidine is slightly higher than that of ASA. They include: diarrhoea, nausea, gastrointestinal upset, bleeding, macro-papular or urticarial rash and, in about 2%, neutropenia. They tend to occur early, within 2–3 months of the therapy. No recent study has been conducted but several studies were performed on ESRD patients in the 1980s showing that statistically fewer patients suffered haemodialysis fistula thrombosis in the ticlopidine-treated groups [9]. A dose of ticlopidine is 2 x 250 mg during meals.

There are some new antiplatelet agents: ticlopidine analogues (PCR 4099 and clopidogrel), P$_2TY$ purinoceptors antagonists (ARL 66096), GPIIb/IIa antagonists (MK-852, SB-214857, pentamidine) and the most promising GP IIb/IIIa antibodies (7E3), but prospective clinical studies are needed to prove their effectiveness in protection of fistula thrombosis.

Don’t forget medical common sense

Prevention of fistula thrombosis should include also such simple measures as keeping the patient and extremity warm, avoiding hypotension, maintaining adequate hydration, discouraging smoking, avoiding excessive pressure over needle sites postdialysis, and self control of the access several times a day.

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