Intrarenal vascular resistance parameters in kidney transplant patients receiving calcineurin inhibitor-based or sirolimus-based regimens

Po-Chu Lee¹, Chih-Yuan Lee², Rey-Heng Hu², Chiao Lo¹, Meng-Kun Tsai² and Po-Huang Lee²

¹Department of General Surgery, National Taiwan University Hospital, Yun-Lin Branch, Yun-Lin County, Taiwan and ²Department of General Surgery, National Taiwan University Hospital, Taipei, Taiwan

Correspondence and offprint requests to: Meng-Kung Tsai; E-mail: fanger2009@gmail.com

Abstract

Background. Use of a calcineurin inhibitor (CNI) immunosuppressant following kidney transplantation is associated with development of vasomotor nephrotoxicity. This study was undertaken to evaluate and compare the influences of CNI-based and CNI-free immunosuppressant regimens on two intrarenal vascular resistance parameters, the resistive index (RI) and the pulsatility index (PI), in renal transplant recipients.

Methods. Forty-nine renal transplant patients who received ultrasonography examination between January 2007 and December 2007 were enrolled in this case-control study. Thirty-one subjects received a CNI-based regimen, and 18 received a CNI-free (sirolimus-based) regimen. RI and PI were determined by duplex Doppler ultrasonography.

Results. Patients receiving a CNI displayed lower cholesterol and triglyceride values and higher RI (mean: 0.7 vs. 0.6, P = 0.002) and PI values (mean: 1.3 vs. 1.1, P = 0.034). Multivariate analyses revealed that advanced age and use of alpha-blockers or diuretics were modestly associated with higher RI and PI values. By multivariate analysis, use of sirolimus was associated with a lower RI by −0.05 [95% confidence interval (CI): −0.085, −0.019; P = 0.003] but not with a lower PI (95% CI: −0.245, 0.001; P = 0.053).

Conclusions. Use of sirolimus is only modestly correlated with a reduced RI and is not associated with a reduced PI. These observations question the superiority of CNI-free over CNI-based regimens with regard to reduction of intrarenal vascular resistance post-transplantation. These findings combined with those regarding recipient factors also cast doubt on the specificity of intrarenal resistance indices for predicting allograft function and/or survival.

Keywords: calcineurin inhibitor; color Doppler ultrasonography; immunosuppressive agents; kidney transplantation; sirolimus

Introduction

Calcineurin inhibitors (CNIs) are notorious for inducing acute and chronic nephrotoxicity [1,2]. CNI-induced modifications of kidney graft function are observed during
early post-transplantation periods, with changes in pre-
glomerular afferent arteriolar vasoconstriction resulting in
pathognomonic histomorphological lesions [2,3]. These
effects are generally reversible upon reduction of CNI dos-
age. Continuous administration is associated with chronic
vascular and tubulointerstitial lesions; further, vascular in-
jury and arteriolar hyalnosis lead to ischaemic glomerular
sclerosis and tubular atrophy. Chronic ischaemia resulting
from vascular obliteration causes stripped interstitial fibro-
sis, a typical and irreversible effect present in ~25% of pa-
tients during the first 6 months post-transplantation [2,4,5].
Biochemical events associated with the nephrotoxic actions of
CNIs include increased endothelin-1 and tumour necrosis
factor beta (TNFβ) production, alterations of the prostag-
landin/thromboxane system, increased renin/angiotensin
system activation and generation of oxidative stress [1]. Al-
though mainly described for cyclosporine A, these events
are also observed with tacrolimus. Avoidance or limited
use of a CNI following renal transplantation is therefore
considered desirable [6].

Uniform criteria for predicting renal impairment during
the early post-transplantation period have not been estab-
lished. However, duplex Doppler ultrasonography, original-
ly introduced to screen for non-vascular diseases of native
kidneys, has been found effective for identifying various
causes of graft insufficiency at early post-transplantation
times [7]. Serial determinations of resistive (RI) and pulsa-
tility (PI) indices with this technique allow estimation of
the degree of interstitial oedema and intrarenal vascular
impedance. After obtaining spectra from segmental arteries
at five representative locations, RI and PI are calculated as
follows [8]:

\[
RI = \frac{\text{peak systolic frequency shift} - \text{minimum diastolic frequency shift}}{\text{peak systolic frequency shift}}
\]

\[
PI = \frac{\text{peak systolic frequency shift} - \text{minimum diastolic frequency shift}}{\text{mean frequency shift}}
\]

The average RI and PI values are then computed to
yield overall RI and PI values. Consideration of maxi-
mum RI and PI values is proposed to improve diagnostic
efficacy as early as 5 days post-transplantation [9]. Evalua-
tion depends mainly on arterial blood flow during di-
astole [10,11]; flow may be disturbed due to increased
intrarenal resistance or may be absent in conditions such
as acute tubular necrosis. Using duplex Doppler ultraso-
nography, the acute narrowing of intrarenal vessels in re-
ponse to CNI treatments has been shown to be rapidly
reversible [12]. Changes in RI and PI have been found to
 correlate with changes in renal vascular resistance, renal
blood velocity and wall shear stress before and 1 month
after percutaneous transluminal angioplasty and stenting
in subjects with renal artery stenosis [13]. This approach
has also been used to demonstrate that ischaemic injury
occurring prior to organ harvesting plays a dominant role
in determining intrarenal resistance in the early post-
transplantation period [11]. Although PI and RI eleva-
tions may be attributable to various causes, including
age of donor and recipient, ureteral obstruction, extrare-
nal graft compression and vasomotor changes induced by
pharmacologic agents, RI values of 0.80 or higher are
closely associated with allograft failure or recipient death
[10,14]. RI and PI measurements are therefore expected
to reveal the presence of allograft nephropathy during the
early post-transplantation period without a need for biopsy.

The immunosuppressive effects of CNIs are mediated
by inhibition of T-cell activation through suppression of the
calcineurin-catalysed dephosphorylation required for
nuclear factor of activated T cell (NFAT)-dependent induc-
tion of cytokine genes. Whether CNI-induced nephrotoxi-
city is secondary to suppression of the calcineurin-NFAT
pathway remains to be established [2]. Nonetheless, sirol-
mus (rapamycin, SRL), an immunosuppressant with a dif-
ferent mechanism of action, is not currently thought to
impair the function of an uninjured kidney [15]. SRL is
widely used for its ability to prolong short- and long-term
graft survival and for its efficacy when combined with
other antiproliferative drugs [16]. The objective of this
study was to examine the influences of recipient factors
and of CNI-free, as compared to CNI-based, immunosup-
pressant regimens on intrarenal vascular resistance para-
meters in renal transplant patients through use of duplex
Doppler ultrasonography. To our knowledge, this study is
the first to evaluate intrarenal vascular impedance in kid-
ney transplant recipients with respect to treatment without,
compared to with, a CNI. It was hypothesized that use of
SRL would result in significantly lower RI and PI values.

**Subjects and methods**

Between January 2007 and December 2007, consecutive patients who
had sustained a renal transplant for at least for 1 year and who displayed
relatively acceptable renal function were followed at our patient depart-
ment and considered for inclusion in this case-control study. Exclusion
criteria were graft infection, acute pyelonephritis, acute urinary infection
and graft rejection. The procedures followed were in accordance with
the ethical standards of our institutional committee on human experi-
mentation and with the Helsinki Declaration of 1975, as revised in 2000.

A total of 49 kidney transplant recipients were included. Subjects re-
ceived an immunosuppressant regimen either containing a CNI (CNI
group, cyclosporine A or tacrolimus, n = 31) or lacking a CNI (SRL
group, n = 18) for a treatment period of more than six months. Subjects
were not randomly assigned to groups but were treated according to the
preferences of their attending physicians. SRL was prescribed either as
the initial immunosuppressant or for rescue or substitution purposes.
The period from renal transplantation to performance of graft ultra-
sonography in the CNI group was between 13 and 90 months and in
the SRL group was between 18 and 85 months. Target cyclosporine
A trough concentrations were 150–180 ng/mL. Target tacrolimus trough
concentrations were 8–10 ng/mL, and target SRL trough concentrations
were 5–10 ng/mL. Doppler ultrasonography was performed every
3 months post-transplantation. No acute or chronic rejections were ob-
served at the time of examination. The presence of underlying diabetes,
hypertension or other systemic diseases was recorded. Body weight, sys-
tolic and diastolic blood pressures, degree of proteinuria and white
blood cell count were measured regularly and recorded. Blood urea ni-
trogen (BUN), creatinine, proteinuria, glomerular filtration rate (GFR),
blood glucose, cholesterol, triglyceride and uric acid values were also
determined routinely and recorded.

All Doppler ultrasonographic measurements were performed by the
same operator using an HDI-5000 ultrasound scanner (Advanced Tech-
nology Laboratories, Bothell, WA) and a 2–50 MHz convex array broad-
band transducer. All analyses were performed between 2:00 and 4:00 p.m.
Because the RI relative to the CNI dose has been observed to rise in the
1–2 h period following administration of cyclosporine A [17], sonogra-
phy was performed on all patients at least 6 h after mediation. Intrahepatic
Doppler signals were obtained from three to four representative proximal
segmental arteries (the first vessels branching off the main renal artery).
Intrarenal vascular resistance parameters in kidney transplant patients receiving calcineurin inhibitor-based or sirolimus-based regimens

Table 1. Characteristics of 49 kidney transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>CNI group (n = 31)</th>
<th>SRL group (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.9 (17.5, 59.2)</td>
<td>50.2 (42.2, 53.8)</td>
<td>0.187</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 (20.6, 25.1)</td>
<td>22.8 (21.0, 24.3)</td>
<td>0.975</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (12.9)</td>
<td>4 (22.2)</td>
<td>0.443</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (61.3)</td>
<td>13 (72.2)</td>
<td>0.438</td>
</tr>
<tr>
<td>ACEI therapy</td>
<td>2 (6.5)</td>
<td>1 (5.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>β-Blocker therapy</td>
<td>9 (29.0)</td>
<td>4 (22.2)</td>
<td>0.743</td>
</tr>
<tr>
<td>Ca-Blocker therapy</td>
<td>5 (16.1)</td>
<td>10 (55.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>α-Blocker therapy</td>
<td>3 (9.7)</td>
<td>1 (5.6)</td>
<td>0.100</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>1 (3.2)</td>
<td>2 (11.1)</td>
<td>0.546</td>
</tr>
<tr>
<td>Urinary WBC (HPF)</td>
<td>0.162</td>
<td>0.162</td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>25 (80.6)</td>
<td>18 (100.0)</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>6 (19.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>195.0 (181.0, 218.0)</td>
<td>229.50 (199.0, 244.0)</td>
<td>0.046</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>164.50 (117.0, 233.0)</td>
<td>164.50 (117.0, 233.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.3 (5.5, 6.8)</td>
<td>5.5 (4.8, 7.1)</td>
<td>0.180</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>18.6 (15.9, 21.5)</td>
<td>17.6 (13.6, 26.3)</td>
<td>0.934</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 (0.9, 1.2)</td>
<td>1.3 (1.1, 1.5)</td>
<td>0.133</td>
</tr>
<tr>
<td>Proteinuria ≥ 100 mg/dL</td>
<td>10.00</td>
<td>10.00</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>72.2 (52.9, 88.1)</td>
<td>52.2 (41.1, 81.6)</td>
<td>0.254</td>
</tr>
<tr>
<td>Fasting blood</td>
<td>91.0</td>
<td>95.5</td>
<td>0.543</td>
</tr>
<tr>
<td>glucose (mg/dL)</td>
<td>83.0 (80.8, 108.0)</td>
<td>85.0 (80.9, 109.0)</td>
<td></td>
</tr>
<tr>
<td>Resistance index</td>
<td>0.7 (0.7, 0.7)</td>
<td>0.6 (0.6, 0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>1.3 (1.2, 1.5)</td>
<td>1.1 (1.0, 1.2)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Continuous data are presented as medians (interquartile range) and categorical data are expressed as numbers (percentage). CNI, calcineurin inhibitor; SRL, sirolimus; BMI, basal metabolic index; ACEI, angiotensin-converting enzyme inhibitor; Ca, calcium; WBC, white blood cells; BUN, blood urea nitrogen; HPF, high-power field.

Discussion

The present study is the first to employ color Doppler ultrasonography to evaluate intrarenal vascular parameters in kidney transplant patients receiving either CNI-free (SRL-containing) or CNI-based immunosuppressant regimens. As anticipated, recipient factors of advanced age and requirement for diuretics or α-blockers were correlated with higher RI and PI values. Surprisingly, however, the CNI-free regimen was found to be only modestly correlated with lower RI values and was not significantly correlated with reduced PI values. These observations cast doubt on the superiority of CNI-free over CNI-containing regimens for reducing intrarenal vascular resistance post-transplantation and also question the specificity of intrarenal resistance parameters in kidney transplant patients receiving calcineurin inhibitor-based or sirolimus-based regimens.
Table 2. Regression analysis of the RI for 49 kidney transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.003 (0.002, 0.005)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male</td>
<td>−0.004 (−0.045, 0.038)</td>
<td>0.854</td>
</tr>
<tr>
<td>BMI (kg/m)</td>
<td>0.003 (−0.003, 0.009)</td>
<td>0.359</td>
</tr>
<tr>
<td>SRL</td>
<td>−0.061 (−0.099, −0.023)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Graft age (months)</td>
<td>−0.001 (−0.001, 0.001)</td>
<td>0.257</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.034 (−0.019, 0.088)</td>
<td>0.202</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.011 (−0.031, 0.053)</td>
<td>0.611</td>
</tr>
<tr>
<td>ACEI therapy</td>
<td>−0.019 (−0.102, 0.065)</td>
<td>0.658</td>
</tr>
<tr>
<td>β-Blocker therapy</td>
<td>0.029 (−0.016, 0.074)</td>
<td>0.200</td>
</tr>
<tr>
<td>Ca-Blocker therapy</td>
<td>−0.012 (−0.056, 0.031)</td>
<td>0.573</td>
</tr>
<tr>
<td>α-Blocker therapy</td>
<td>0.085 (0.016, 0.155)</td>
<td>0.017*</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>0.068 (−0.014, 0.150)</td>
<td>0.101</td>
</tr>
<tr>
<td>Urinary WBC &gt;5/HPF(^b)</td>
<td>0.059 (0.000, 0.118)</td>
<td>0.051</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>0.000 (0.000, 0.000)</td>
<td>0.958</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.000 (0.000, 0.000)</td>
<td>0.628</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>0.009 (−0.006, 0.023)</td>
<td>0.237</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>0.002 (−0.001, 0.005)</td>
<td>0.206</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>−0.002 (−0.053, 0.050)</td>
<td>0.952</td>
</tr>
<tr>
<td>GFR(^c)</td>
<td>−0.001 (−0.001, 0.001)</td>
<td>0.854</td>
</tr>
<tr>
<td>Proteinuria ≥100 mg/dL</td>
<td>0.032 (−0.051, 0.116)</td>
<td>0.440</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>0.001 (0.000, 0.002)</td>
<td>0.110</td>
</tr>
</tbody>
</table>

Double dashes (−) indicate that the variable was not included in the multivariate linear regression analysis. CI, confidence interval; SRL, sirolimus; BMI, basal metabolic index; ACEI, angiotensin-converting enzyme inhibitor; Ca, calcium; WBC, white blood cells; BUN, blood urea nitrogen; NA, not applicable; HPF, high-power field.

\(^a\)Significantly correlated with RI; \(^b\)As compared to subjects with urinary WBC counts ≤5/HPF.

\(^c\)GFR, glomerular filtration rate (Walser formula) = 7.57 × (S.Cr × 0.0884)\(^{-1}\) – 0.103 × age + 0.096 × weight – 6.66 (for males), = 6.05 × (S.Cr × 0.0884)\(^{-1}\) – 0.080 × age + 0.080 × weight – 4.81 (for females).

Table 3. Regression analysis of the PI for 49 kidney transplant recipients

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.013 (0.007, 0.018)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male</td>
<td>0.013 (−0.138, 0.163)</td>
<td>0.865</td>
</tr>
<tr>
<td>BMI (kg/m)</td>
<td>0.015 (−0.008, 0.038)</td>
<td>0.204</td>
</tr>
<tr>
<td>SRL</td>
<td>−0.151 (−0.296, −0.005)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Graft age (months)</td>
<td>−0.002 (−0.004, 0.001)</td>
<td>0.142</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.149 (−0.045, 0.342)</td>
<td>0.129</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.018 (−0.136, 0.172)</td>
<td>0.815</td>
</tr>
<tr>
<td>ACEI therapy</td>
<td>−0.070 (−0.376, 0.235)</td>
<td>0.644</td>
</tr>
<tr>
<td>β-Blocker therapy</td>
<td>0.117 (−0.045, 0.280)</td>
<td>0.153</td>
</tr>
<tr>
<td>Ca-Blocker therapy</td>
<td>0.008 (−0.151, 0.167)</td>
<td>0.919</td>
</tr>
<tr>
<td>α-Blocker therapy</td>
<td>0.291 (0.037, 0.545)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td>0.363 (0.076, 0.650)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Urinary WBC &gt;5/HPF(^b)</td>
<td>0.195 (−0.021, 0.411)</td>
<td>0.076</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>0.000 (−0.001, 0.002)</td>
<td>0.685</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>0.000 (0.000, 0.001)</td>
<td>0.223</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>0.050 (−0.002, 0.103)</td>
<td>0.059</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>−0.005 (−0.006, 0.016)</td>
<td>0.396</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.025 (−0.162, 0.213)</td>
<td>0.787</td>
</tr>
<tr>
<td>GFR(^c)</td>
<td>−0.001 (−0.003, 0.003)</td>
<td>0.969</td>
</tr>
<tr>
<td>Proteinuria ≥100 mg/dL</td>
<td>0.177 (−0.125, 0.478)</td>
<td>0.244</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>0.002 (−0.001, 0.005)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Double dashes (−) indicate that the variable was not included in the multivariate linear regression analysis. CI, confidence interval; SRL, sirolimus; BMI, basal metabolic index; ACEI, angiotensin-converting enzyme inhibitor; Ca, calcium; WBC, white blood cells; BUN, blood urea nitrogen; NA, not applicable; HPF, high-power field.

\(^a\)Significantly correlated with PI; \(^b\)As compared to subjects with urinary WBC counts ≤5/HPF.

\(^c\)GFR, glomerular filtration rate (Walser formula) = 7.57 × (S.Cr × 0.0884)\(^{-1}\) – 0.103 × age + 0.096 × weight – 6.66 (for males), = 6.05 × (S.Cr × 0.0884)\(^{-1}\) – 0.080 × age + 0.080 × weight – 4.81 (for females).
Intrarenal vascular resistance parameters in kidney transplant patients receiving calcineurin inhibitor-based or sirolimus-based regimens

Although previous studies have not supported a close relationship between RI and PI values and the degree of short-term or long-term allograft function [18], an association between high RI and PI values and normal kidney function appears to be rare. Cutoff values of RI >0.8 and of PI >1.8 are generally characteristic of both allograft failure and death with a functioning graft [14] but are not pathognomonic. In the present study, as well as in other studies [14,19,20], extrarenal characteristics of kidney recipients such as age and presence of hypertension were found to correlate more strongly with RI and PI values than did use of CNIs or anti-hypertensive agents. RI and PI values are therefore proposed to reflect more accurately the compliance of the central arteries of the recipient rather than allograft properties or vasculature. This appears to be the case for the higher intrarenal blood flow parameters characteristically observed in older recipients, especially those with hypertension [21]. Furthermore, elevations in RI and PI values have been attributed to atherosclerosis-reduced pre-renal aortic compression chamber function, to vascular stiffness, and to increased intima-media thickness secondary to ageing and end-stage renal disease rather than to impaired allograft function per se [22,23]. Whether catecholamine infusions, diuretics or alpha-blockers were administered to subjects of these studies because of post-transplantation circulatory impairments or ischaemia, as represented by higher RI and PI values, or because of hypotensive episodes and circulatory impairments present prior to transplantation is difficult to ascertain. Regardless, traditional cardiovascular risks are known to be correlated with RI values and account for ~50% of deaths of patients with functioning grafts [24].

The implications of the present findings regarding SRL-containing regimens to allograft function or survival are unclear. However, the significantly lower RI (P = 0.003) and lower but statistically insignificant PI (p = 0.053) associated with use of SRL may be theoretically explained by the ability of this immunosuppressant to attenuate immune-obliterative arterial and arteriolar pathophysiological processes characteristic of CNIs. Whereas CNIs induce constriction of the afferent arteriole proximal to the glomerulus [25] and accumulation of nodular hylaine deposits in the media conducive to obliterator arteriolopathy, SRL has been shown to decrease arterial intimal thickening in cynomolagus monkey recipients of allografts [26]. The observed association of SRL use with a lower RI must nevertheless be interpreted with caution, as the administration of alpha-, beta- and calcium channel blockers was not accounted for during the multivariate regression analyses. In this regard, it is of interest that no correlation between use of a CNI in stable kidney patients and higher RI and PI values, irrespective of the use of antihypertensive agents, was observed by other investigators [14,19,20]. These findings further serve to highlight the non-specificity of intrarenal resistance indices as determinants of allograft function or survival.

Estimated graft function with SRL-based immunosuppression has been found superior to CNI-based immunosuppression at 1 year post-transplantation [27]. However, it should be noted that, although SRL-based regimens are not associated with vasomotor nephrotoxicity, SRL may not be entirely without renal effects [15]. For example, this inhibitor of the mammalian target of rapamycin has been observed to exacerbate the nephrotoxicity occurring in response to large doses of CNIs in animal model studies and in phase III trials in human renal transplantation. Furthermore, certain findings with animal models and reports of non-randomized experiences at single centres are consistent with the hypothesis that SRL delays recovery from a tubular injury. However, this hypothesis has not been confirmed by randomized, multi-center and larger single-centre studies. A relatively small fraction of subjects treated with SRL de novo may exhibit prolongation of delayed graft function. Finally, SRL-based immunosuppression is associated with an increased frequency of semiquantitative proteinuria [27].

Certain limitations of the present study are acknowledged. Firstly, protocol biopsies were not performed routinely; renal biopsies were performed only when the possibility of rejection was suspected. Secondly, the conditions of each individual graft were not determined. Because such determinations are extremely difficult and laborious, graft conditions were evaluated in terms of age, BUN, GFR and proteinuria. Thirdly, the findings presented here derive from a relatively small sample number. At the present time, data has been collected from 60 patients; the study is ongoing with expansion of the data base considered a primary long-term objective. With a larger sample number, it should also prove feasible to ascertain whether the CNI inhibitors cyclosporine A and tacrolimus differentially alter intrarenal vascular resistance parameters in kidney transplant recipients.

In conclusion, findings of the present study confirm that recipient factors of advanced age and requirement for diuretic or alpha-blocker therapy correlate with increased RI and PI values in kidney transplant recipients. However, use of an SRL-based regimen was found to be correlated only modestly with lower RI and not with lower PI values. The latter findings do not provide conclusive evidence for the superiority of CNI-free as compared to CNI-based regimens in terms of reducing intrarenal vascular resistance post-transplantation and highlight the non-specificity of intrarenal resistance indices for predicting allograft function or survival.

Acknowledgements. None.

Conflict of interest statement. None declared.

References
Benefit of kidney transplantation beyond 70 years of age

Kristian Heldal1,2,3, Anders Hartmann2,3, Diana C. Groøtendorst4, Dinanda J. de Jager4, Torbjørn Leivestad5, Aksel Foss6 and Karsten Midtvedt2

1Section of Nephrology and Endocrinology, Clinic of Internal Medicine, Sykehuset Telemark, Norway, 2Section of Nephrology, Medical Department, Oslo University Hospital Rikshospitalet, Norway, 3Faculty of Medicine, University of Oslo, Norway, 4Department of Clinical Epidemiology, Leiden University Medical Centre, The Netherlands, 5Institute of Immunology, Oslo University Hospital Rikshospitalet, Norway and 6Division of Surgery, Section for Transplantation, Oslo University Hospital Rikshospitalet, Norway

Correspondence and offprint requests to: Kristian Heldal; E-mail: kristian.heldal@sthf.no; kri-held@online.no

Abstract
Background. Kidney transplantation generally improves long-term survival in patients with end-stage renal disease. However, in patients older than 70 years of age, only limited data are available that directly compare the potential survival benefit of transplantation versus dialysis.

Methods. All patients aged above 70 years who started dialysis between 1990 and 2005 and were waitlisted for kidney transplantation were included in the study. They