Central aortic pressure augmentation in stable renal transplant recipients

CHARLES J. FERRO, TESSA SAVAGE, SARAH J. PINDER, and CHARLES R.V. TOMSON

The Richard Bright Kidney Unit, Southmead Hospital, Bristol, England, United Kingdom

Central aortic pressure augmentation in stable renal transplant recipients.

Background. Premature cardiovascular disease is the leading cause of death in renal transplant recipients and classical risk factors significantly underestimate the risk. The increased effect of arterial wave reflections on central arteries has recently been shown to be an important independent predictor of cardiovascular mortality in chronic hemodialysis patients. The aim of this study was to assess the contribution of several classical and potential non-classical cardiovascular risk factors on aortic pressure augmentation by the reflected arterial wave in stable renal transplant recipients.

Methods. Using the non-invasive technique of pulse wave analysis aortic augmentation was investigated in 250 stable renal transplant recipients. Peripheral pulse waveforms were recorded from the radial artery. Central aortic waveforms were then generated and the aortic augmentation index calculated.

Results. In multivariate analysis, female sex (regression coefficient 7.5 ± 1.7%; \( P < 0.001 \)), heart rate (−4.8 ± 0.5% per 10 beats/min; \( P < 0.001 \)), mean arterial pressure (4.2 ± 0.6% per 10 mm Hg; \( P < 0.001 \)), the persistence of an arteriovenous waveform [4], total time on renal replacement therapy (3.8 ± 0.9% per 10 years; \( P < 0.001 \)), height (−3.1 ± 0.8% per 10 cm; \( P < 0.001 \)), immunosuppression with cyclosporine (2.8 ± 1.3%; \( P < 0.005 \)) and age (2.5 ± 0.5% per 10 years; \( P < 0.001 \)) were all important correlates of aortic augmentation index.

Conclusions. Our findings suggest, to our knowledge for the first time, that both the presence of a functioning arteriovenous fistula and immunosuppressive treatment with cyclosporine are associated with an increased aortic augmentation index in renal transplant recipients and could, therefore, be potential reversible contributors to the high cardiovascular risk profile in these patients.

Premature cardiovascular disease is the leading cause of death in renal transplant recipients and as a consequence, one of the leading causes of renal allograft failure [1]. Thus, better management of cardiovascular disease and its risk factors potentially could improve both recipient and graft survival. However, despite the abundance of evidence relating to the management of cardiovascular risk in the non-renal population, the evidence base available for the rational management of cardiovascular risk in renal transplant recipients is small.

Enhanced augmentation of the central aortic systolic pressure by the increased effect of arterial wave reflections, as defined by the augmentation index (AIx), has recently been shown to be a powerful predictor of cardiovascular and all cause mortality in patients on chronic hemodialysis (Fig. 1) [2]. The technique of central pulse wave analysis employs applanation tonometry to record the pressure wave from the radial artery accurately [3], and a well-validated generalized transfer factor can then be used to generate the corresponding aortic arterial waveform [4]. From this, AIx can be assessed non-invasively and reproducibly [5, 6].

Classical risk factors do not account for the totality of cardiovascular risk in renal transplant recipients. A recent study found that the Framingham Heart Study-based cardiovascular risk equation significantly underestimated the risk of ischemic heart disease in renal transplant recipients [7]. These findings suggest that other factors, in particular non-classical cardiovascular risk factors, may play a significant role in the increased cardiovascular risk observed in these patients. Identification of these non-classical risk factors might help target interventions to reduce the high incidence of cardiovascular events observed in renal transplant recipients. The aim of this study was to assess the impact of several classical cardiovascular risk factors, immunosuppressive agents, renal function and the presence of an arteriovenous (A-V) fistula on AIx in a large cohort of stable renal transplant recipients.

METHODS

Patients

Two hundred and fifty patients who had a working renal transplant and whose creatinine clearance had not

Key words: arterial wave reflection, kidney transplant, calcineurin inhibitors, arteriovenous fistula, cardiovascular disease.

Received for publication November 7, 2001
and in revised form February 12, 2002
Accepted for publication February 14, 2002
© 2002 by the International Society of Nephrology
Aortic pressure. AIx represents the difference between the first and second peaks of the central pressure waveform in systole (Fig. 1), expressed as a percentage of the pulse pressure. Values are reported as the mean of two stable readings.

**Data analysis**

Statistical analysis was performed with SPSS version 8.0 for windows (SPSS Inc, Chicago, IL, USA). A multiple linear regression model was derived for AIx using stepwise regression analysis. Factors introduced into the model were sex, age, height, weight, heart rate, mean blood pressure, left ventricular ejection time (LVET), smoking and diabetic history, presence of a functioning A-V fistula, immunosuppression with cyclosporine, tacrolimus or a non-calcineurin inhibitor based regime, anti-hypertensive and cholesterol lowering medication, serum total cholesterol, albumin, calcium and phosphate concentrations, hemoglobin concentration, calculated creatinine clearance, months from current transplant and total time on renal replacement therapy. Factors that were not significant were excluded from the model. The final model was checked for normality by plotting the residuals. Results are means ± standard deviations or medians (interquartile ranges). Normally distributed variables changed by more than 5 mL/min for at least three months were analyzed by unpaired t tests or analysis of variance (ANOVA). Variables that were not normally distributed were analyzed by Mann-Whitney U or Kruskal-Wallis non-parametric tests. Frequency differences were tested by the $\chi^2$ test. A $P$ value of <0.05 was considered statistically significant.

**RESULTS**

Two subjects were excluded from the analysis because of incomplete data being available. Both cases were wheelchair bound and, therefore, their height could not be accurately measured. Inclusion of these two patients by estimating their height did not make any significant impact on the analysis. The demographics of the group are shown in Tables 1 and 2 with patients divided by persistence of arteriovenous (AV) fistula and immunosuppressive regime, respectively. All but two of the patients taking cyclosporine were on the Neoral formulation (Novartis, Surrey, UK).

In multivariate analysis, gender, heart rate, mean arterial pressure (MAP), the presence of a functioning A-V fistula, total time on renal replacement therapy, height, use of cyclosporine in the immunosuppressive regime and age were important correlates of AIx (Table 3). Together these variables accounted for 60% of the variance. The mean values for AIx in patients with and without a persistent AV fistula and on different immunosuppression regimes are shown in Figure 2. Diabetes, creatinine clearance, albumin, hemoglobin, smoking his-

---

**Peripheral blood pressure measurement**

Brachial artery blood pressure was measured in duplicate using a validated oscillometric technique (HEM-705CP; Omron) [8] or using a mercury sphygmomanometer according to the recommendations of the British Hypertension Society [9]. Values are reported as the mean of two stable readings.

**Pulse wave analysis**

Central pressure waveforms were derived and analyzed using the technique of pulse wave analysis (SphygmoCor; PWV Medical, Sydney, Australia) as previously described [5, 6, 10]. In brief, a high fidelity micromanometer (SPC-301; Millar Instruments, TX, USA) was used by an experienced operator (CJF) to flatten, but not occlude, the radial artery by using gentle pressure with the wrist slightly extended and supported on a pillow. Data were collected directly into a portable computer and, after 11 seconds of data capture, an averaged peripheral waveform and a corresponding central waveform were generated. The central waveform was then analyzed using the system software to determine AIx and central
therapy, weight, total cholesterol level, calcium phosphate product, LVET and use of antihypertensive or lipid lowering medication were not significant determinants. Results for the coefficients in the equation (Table 3) are expressed in clinically meaningful units of measurement. Time from current transplant was excluded from the final model using stepwise regression, most likely because of its correlation with time on renal replacement therapy ($r = 0.76$, $P < 0.0001$). If time on renal replacement therapy was not included in the model, time from current transplant became an independent predictor of variation in AIX (coefficient $4.8 \pm 1.0\%$; $P < 0.001$) with the other correlates remaining unchanged.

**DISCUSSION**

The results show that three non-classical risk factors for cardiovascular disease—the persistence of an A-V
Table 3. Multiple linear regression analysis with augmentation index as the dependent variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>7.5</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>10 bpm</td>
<td>-4.8</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>10 mm Hg</td>
<td>4.2</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A-V fistula</td>
<td>Persistent</td>
<td>4.1</td>
<td>1.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Time on RRT</td>
<td>10 years</td>
<td>3.8</td>
<td>0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height</td>
<td>10 cm</td>
<td>-3.1</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Yes</td>
<td>2.8</td>
<td>1.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Age</td>
<td>10 years</td>
<td>2.5</td>
<td>0.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted R² value for the entire study group, 0.6, P < 0.001. Abbreviations are: bpm, beats per minute; MAP, brachial mean arterial pressure; AV, arteriovenous; RRR, renal replacement therapy.

fistula, time on renal replacement therapy and treatment with cyclosporine—are important contributors to AIX. In addition to these factors, our study confirmed that gender, heart rate, blood pressure, height and age remain important determinants of AIX in renal transplant recipients. The contribution made by these factors to AIX is very similar to that observed in healthy subjects [11]. Indeed, an increase of 10 beats per minute in heart rate in our study produced a decrease in AIX of 5%, which is very similar to the percentage found in an interventional study using patients with cardiac pacemakers in which AIX decreased by 4% for every 10 beats per minute increase in heart rate [12].

Augmentation index is often considered to be an index of arterial stiffening. However, AIX depends on many factors including pulse wave velocity, traveling distance of pressure waves (body height), ejection duration, and the reflective properties of the arterial system. Arterial stiffening increases pulse wave velocity and influences transit times of pressure waves (Tr in Fig. 1). Arterial stiffening, therefore, reduces Tr from the peripheral reflective sites toward the ascending aorta, thereby altering the timing of incident and reflective waves. The intensity of wave reflection is dependent on the reflective properties of the vascular tree that could be altered independently of vascular stiffening [13]. The peripheral reflectance is influenced by physical properties, vasomotor tone and the number of smaller resistance arteries [13]. Several abnormalities in the microcirculation of renal failure patients have been reported including decreased endothelium-mediated vasodilation in cyclosporine-treated transplant recipients [14]. Using pulse wave analysis, it is currently not possible to distinguish the relative contributions made by large or small vessel pathology to the measured AIX.

An increased effect of wave reflections on the aorta causes increased pressure during systole increasing left ventricular workload and promoting left ventricular hypertrophy [15], a strong independent predictor for all-cause mortality [16]. Early return of the reflected wave also results in decreased diastolic tension-time index [15, 17]. These alterations increase left ventricular oxygen requirements and predispose to left ventricular hypertrophy. The reduced diastolic tension-time index contributes to modifications of coronary perfusion with relative subendocardial ischemia [15, 18]. Therefore, it is perhaps not surprising that AIX has been found to have a strong association with echographically measured left ventricular hypertrophy [10] and has been found to be a powerful predictor of cardiovascular and all-cause mortality in hemodialysis treated patients [2].

We found the persistence of a functioning A-V fistula to be associated with a higher AIX in this population.
The creation of an AV fistula for hemodialysis access lowers systemic vascular resistance and results in an increase in cardiac output in order to maintain blood pressure [19]. A sustained increase in cardiac output and arterial flow is associated with dilation and hypertrophy of large conduit arteries [20]. Moreover, a persistent increase in cardiac output, by the mechanism of myogenic autoregulation of peripheral blood flows, can lead to a secondary increase in peripheral resistances and remodeling of small resistance arteries [21]. These alterations in vascular structure and function have a negative feedback on left ventricular afterload, increasing the aortic impedance [22]. The enlargement of large conduit arteries increases the inertial effect of the blood mass, the hypertrophy of arterial walls increases the stiffness of the arteries, and the remodeling of the resistance arteries increases the peripheral resistance. These effects serve to increase AIx, as observed in our study. Furthermore, these changes in circulatory hemodynamics lead to left ventricular hypertrophy as an adaptive response to a long-term increase in volume and pressure overload. Indeed, left ventricular mass decreases significantly in renal transplant patients after closure of an AV fistula with no observed change in blood pressure [23]. Whether AIx would decrease, or indeed cardiovascular risk improve after closure of an AV fistula is still to be determined. However, rather intriguingly, the presence of a previous AV fistula has been found to be associated with fatal and nonfatal cardiac events perioperatively during the AV fistula creation [24], suggesting that the presence of an AV fistula is indeed a non-classical cardiovascular risk factor.

Hypertension occurs in approximately 80% of patients on cyclosporine following renal transplantation [25]. Using multivariate analysis to correct for blood pressure, we found cyclosporine—but not tacrolimus—to be associated with a higher AIx, despite both agents being calcineurin inhibitors and being thought of as having similar actions. Indeed, compared with patients on tacrolimus, patients on cyclosporine had a markedly raised AIx (Fig. 2). Cyclosporine also has been found to predispose to left ventricular hypertrophy more so than would be expected from the higher associated blood pressure [26], a finding that could be explained, at least in part, by the association we have found between cyclosporine treatment and higher AIx.

The pathophysiology of cyclosporine-induced hypertension is not yet known. Several possible mechanisms have been proposed including sodium retention, raised circulating endothelin levels, transforming growth factor-β (TGF-β) mediated endothelin synthesis, altered prostaglandin production, impaired basal production of nitric oxide, increased plasma renin activity and activation of the sympathetic nervous system [14]. It seems likely that one or more of these mechanisms may be responsible for the increased AIx observed in the cyclosporine treated patients in our study. Interestingly, there was no significant difference in Tr between patients on cyclosporine and tacrolimus, suggesting that the increased AIx observed in cyclosporine treated patients is not as a consequence of increased aortic stiffness.

Although cyclosporine and tacrolimus are both calcineurin inhibitors and are thought to have similar intrinsic properties, the incidence of hypertension has been found to be lower in patients treated with tacrolimus compared with cyclosporine treated patients [27]. However, trough tacrolimus levels strongly correlate with total tacrolimus exposure, whereas this correlation is poor for cyclosporine [28]. Thus, it may be easier to stay within the therapeutic target for tacrolimus, which may translate into less post-transplant hypertension and arterial stiffness. All except two of the patients in this study were on the Neoral formulation of cyclosporine, which contains α-tocopherol. From our study we cannot tell whether this antioxidant vitamin affects arterial stiffness in any way. Patients not on a calcineurin inhibitor-based immunosuppressive regime (all were on steroids and azathioipine or mycophenolate mofetil) had similar AIx to patients on cyclosporine. However, these patients had been on renal replacement therapy for a considerably longer period of time (Table 2), which we have shown to increase AIx. In our cohort, patients would have been on tacrolimus only if they had a mismatch at the DR locus, on a second or subsequent transplant, or had an episode of rejection while on the cyclosporine treatment. Although we believe it to be unlikely, it is possible that any of these factors could in some way account for the increased AIx observed in patients on cyclosporine compared to those on tacrolimus.

Diabetes mellitus has been shown to increase AIx in some [29, 30], but not all [31] studies. It appears that any effects of diabetes mellitus may have been masked by the other factors relating to this cohort. Furthermore, only 10% of our cohort had diabetes mellitus (Table 2), and any small effect may have been missed. Creatinine clearance was not associated with AIx in our group of patients. Creatinine clearance has been shown to be associated with arterial stiffness but only in subjects with plasma creatinine concentrations well within the normal range [32]. From our study it would appear that length of exposure to uremia is a much more important factor than renal function after transplantation. Neither total serum cholesterol nor treatment with a statin was associated with AIx in this study. Although increased arterial stiffness has been shown in hypercholesterolemics [33], most of our study population had a total cholesterol value within the normal range (Table 2) and thus any small interaction may have been missed. Similarly, hyperparathyroidism has been associated with increased AIx [34], but most of our patients had calcium phosphate...
products within the normal range. Not enough patients
in this study had their serum parathyroid hormone as- sayed for any meaningful statistical analysis to be per-
formed.

In conclusion, we have found that both having a function- ing A-V fistula and being on cyclosporine are associ-
ated with having a higher AIx and, therefore, are poten-
tially treatable factors that if addressed could result in
lower cardiovascular morbidity and mortality in this high
risk population. Longitudinal studies are needed to show
whether these factors are indeed non-classical cardiovas-
cular risk factors.

ACKNOWLEDGMENTS

The results of this study were presented in part at the 2001 ASN-
ISN World Congress in San Francisco, USA.

Reprint requests to Dr. Charles J. Ferro, Richard Bright Kidney Unit,
Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, England,
United Kingdom.
E-mail: charlesferro@hotmail.com

REFERENCES

313, 2000
37:1434–1439, 2001
11:1735–1743, 2000
mary. BMJ 319:630–635, 1999
tension 12:1175–1189, 1997
337, 1993
don, Edward Arnold, 1988
docardial ischaemia in dogs with normal coronary arteries. Circ Res
30:67–81, 1972
21. Guyton AC: The body’s approach to arterial pressure regulation, in Circulatory Physiology III: Arterial Pressure and Hypertension,
22. London GM: The concept of ventricular/vascular coupling: Func-
tional and structural alterations of the heart and arterial vessels
23. van Duijnoven ECM, Cheryx ECM, Tordoir JHM, et al: Effect of closure of the arteriovenous fistula on left ventricular dimen-
sions in renal transplant patients. Nephrol Dial Transplant 16:368–
372, 2001
24. Solomonson MD, Johnson ME, Ilstrup D: Risk factors in patients
having surgery to create an arteriovenous fistula. Blood Vessels
31(Suppl 2):S73–78, 1993
26. Gallaisou E, Morris STW, Jardine AG, et al: Cardiac and vascu-
vasoconstriction and systemic hypertension in renal transplant pa-
tients treated with cyclosporin A versus FK 506. Transplant Int
11:3–10, 1998
28. MacDonald AS: Impact of immunosuppressive therapy on hyper-
tension. Transplantation 11:SS70–SS76, 2000
Quart J Med 93:441–448, 2000
93:839–841, 2000
stiffness and thickness in patients with familial hypercholesterole-
doerlin Metab 85:3515–3519, 2000