Acute effect of haemodialysis on arterial stiffness: membrane bioincompatibility?

Adnan Mourad, Shane Carney, Alastair Gillies, Bernard Jones, Ranjit Nanra and Paul Trevillian

Department of Nephrology, John Hunter Hospital, Locked Bag 1, Hunter Region Mail Centre, NSW 2310, Australia

Abstract

Background. Repetitive endothelial damage from dialysis membrane incompatibility is a probable cause of accelerated atherosclerosis in haemodialysis patients. Consequently pulse wave velocity (PWV), a measure of arterial stiffness, was utilized as a surrogate marker of vascular dysfunction during dialysis with two commonly used synthetic dialysers.

Methods. PWV was monitored before, during and after haemodialysis using both polysulphone and polyamide membranes. PWV, an arterial stiffness measure, was calculated from the carotid to the femoral (C-F) and also to the radial (C-R) artery. In a further group, PWV was monitored while polysulphone and polyamide membranes were perfused with blood without dialysate.

Results. Mean aortic (C-F) PWV was lower during dialysis with the polyamide membrane, being 14 and 16% less following 75 and 135 min of dialysis ($P < 0.05$) in 24 patients. Because intradialytic intravascular volume changes alter PWV, a subgroup analysis in 11 patients where dialysis fluid removal during both periods was minimal (<1 kg) was performed, and a persistent and significant increase in aortic PWV was detected with the polysulphone kidney being maximal (40%) at 75 min ($P < 0.01$). This increase was negatively correlated with pre-dialysis PWV ($P < 0.01$). In contrast, the polyamide dialysers did not change PWV. An increase in C-R PWV was also noted with the polysulphone membrane ($P < 0.05$). In the nine patients where membranes were perfused with blood without dialysate, aortic PWV was again significantly increased by the polysulphone ($P < 0.01$), but not the polyamide dialysers.

Conclusions. Haemodialysis with polysulphone but not polyamide membranes acutely alters aortic ‘stiffness’, an effect postulated to be due to membrane bioincompatibility. However, factors including age, time on dialysis and underlying vascular disease, were also found to impact on these acute dialysis-induced changes to vascular function. Since these acute changes disappear post-dialysis, their long-term consequences are uncertain.

Keywords: arterial stiffness; bioincompatibility; blood pressure; haemodialysis; pulse wave velocity

Introduction

The high dialysis population cardiovascular mortality rate has become a major issue and is not simply related to the increased acceptance of elderly subjects. A recent cross-sectional haemodialysis study found that while traditional coronary risk factors may apply to this population, other factors including the uraemic milieu and the haemodialysis procedure itself were probably contributory [1]. In particular, the US Renal Data System has provided persuasive evidence that dialysis membrane biocompatibility plays an important role in the poor outcome of chronic haemodialysis patients, the mortality rate being higher with cellulose membranes compared to modified cellulose or synthetic membranes [2]. Haemodialysis causes numerous changes including abnormal complement activation with disordered leukocyte–endothelial interactions, the release of plasma factors including tumour necrosis factor-alpha and reactive oxygen species, the latter causing vascular oxidative stress [3]. Given accumulating evidence that atheroma is an inflammatory disease [4], elevated markers of underlying cytokine burden such as C-reactive protein in maintenance haemodialysis patients [5] may reflect ongoing arterial damage due to bioincompatibility.

Pulse wave velocity (PWV), a non-invasive measure of arterial stiffness was chosen to more directly evaluate the effect of haemodialysis and dialysis membranes on vascular function. Carotid-femoral (C-F) PWV, a measure of aortic stiffness, has recently been shown...
Patients and methods

Study population

Thirty three patients (15 male) on maintenance dialysis with a left forearm arteriovenous fistula were enrolled. Cardiovascular instability during dialysis and current symptomatic cardiovascular disease including angina and cardiac failure were exclusion factors as was nitrate treatment. Patients regularly requiring large intradialytic fluid removal were excluded to avoid volume replacement during dialysis. Patients were allowed to continue anti-hypertensive and lipid-lowering agents. Informed consent was obtained and the double-blind crossover study protocol was approved by the Hunter Area Health Service Human Ethics Committee.

Dialysis protocol

Dialysis was performed thrice weekly on a Gambro AK95 machine in 24 patients. Blood flow rates varied between 250 and 350 ml/min, and the bicarbonate dialysate flow was 500 ml/min. All subjects underwent two routine 4 h dialyses within 1–2 weeks of each other on the same day and at the same time to compare the dialysers. No exogenous plasma volume expanders were used during the study periods. During these sessions, patients were randomly allocated a polysulphone dialyser (Fresenius F6 or F8 HRS), or a polyamide S dialyser (Gambro polyflux 6 or 8L) with the other dialyser being used during the second experimental session. Dialysers were covered to blind the investigator (A.M.) as well as the patient. The subjects’ heart rate, blood pressure (OMRON HEM 705 CP) and PWV were measured 15 min before dialysis and then 15, 75, 135 and 195 min after commencement of dialysis, and repeated 15 min after dialysis completion. Body weight was measured before and after dialysis.

Pre-dialysis protocol

To better define blood and dialysis membrane interactions yet minimize the complicating effects of the dialysis process including altered vascular volume and electrolyte fluxes, a further comparable group of nine patients were studied. Dialysers were perfused at 150 ml/min pre-dialysis over a 60 min period without dialysate, the filtrate being immediately replaced by normal saline. PWV measurements were taken pre-perfusion and at 15, 30, 45 and 60 min on two occasions. Polysulphone and polyamide membranes were again randomly allocated.

Pulse wave velocity

The PWV was measured using an automatic computerized recorder and the results were analysed using the Complior® program (Complior II; Colson, Garges les Genesse, France). Pressure-sensitive transducers were placed over the right carotid, femoral and radial arteries with the patient in the supine position. PWV (m/s) of the C-F and carotid-radial (C-R) territory was calculated by dividing the distance separating the sensors (mm) by the time corresponding to the period separating the start of the rising phase of the carotid pulse wave and that of the femoral and also the radial pulse waves [6]. At least 10 valid signals were averaged to obtain a reading. An intraobserver co-efficient of variation of 5.5% (C-F) and 5.4% (C-R) has been established in our laboratory.

Statistical analysis

Repeated measures analysis of variance was performed to compare readings taken with the polysulphone and polyamide dialysers. Student’s t-test was used to determine at which time points differences occurred and to compare calculated means during and between dialysis days. These were adjusted for multiple testing using the Bonferroni correction. Two-way ANOVA comparing time on dialysis with membrane type was also evaluated. P < 0.05 was considered statistically significant. Results are expressed as mean ± SD.

Results

Dialysis protocol

All subjects completed the study and selected patient characteristics are presented in Table 1. All subjects remained in good health during the brief study period and no dialysis complications occurred in this group of clinically stable patients undergoing a normal dialysis process and continuing to take routine medications. Mean pre-dialysis body weight prior to use of the

<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of 24 maintenance haemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Time on dialysis (months)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
</tr>
<tr>
<td>Hypotensive agents (%)</td>
</tr>
<tr>
<td>Hypolipemic agents (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean weight (kg)</th>
<th>Polysulphone dialysis</th>
<th>Polyamide dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dialysis</td>
<td>60.0 ± 15.5</td>
<td>59.2 ± 15.2</td>
</tr>
<tr>
<td>Post-dialysis</td>
<td>57.8 ± 14.5***</td>
<td>56.9 ± 15.4**</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>108 ± 13</td>
<td>108 ± 14</td>
</tr>
<tr>
<td>Pre-dialysis</td>
<td>98 ± 13**</td>
<td>99 ± 15**</td>
</tr>
<tr>
<td>Mean heart rate (b.p.m.)</td>
<td>74 ± 11</td>
<td>75 ± 13</td>
</tr>
<tr>
<td>Pre-dialysis</td>
<td>74 ± 13</td>
<td>74 ± 11</td>
</tr>
</tbody>
</table>

Mean ± SD.

**P < 0.01.
polysulphone or polyamide dialyser was similar as was the degree of fluid loss during dialysis being 2.2±1.2 and 2.3±1.2 kg, respectively. Mean pre-dialysis blood pressure during the two dialysis procedures also fell to a comparable degree in both groups. Systolic and diastolic blood pressures were also similar (Figure 1).

Mean pre-dialysis PWV was also similar being 12.6±5.0 and 12.8±5.0 m/s (C-F), and 9.0±2.4 and 8.9±1.7 m/s (C-R) preceding the respective polysulphone and polyamide dialysis sessions. During dialysis, a relative reduction in mean aortic C-F PWV was measured with the polyamide dialyser when compared to the polysulphone dialyser which was statistically significant at 75 and 135 min (Figure 2), representing a respective 14 and 16% reduction. Similar relative changes in C-R (subclavian-axillary-brachio-radial) PWV did not achieve statistical significance.

Because of the fall in body weight and concomitant fall in blood pressure that occurred during dialysis in many subjects and the consequent net effects of such changes in acutely reducing PWV, all patients whose body weight fell < 1 kg during the two dialysis periods were analysed separately (subgroup A). There were 11 subjects in this group (six female) and while their mean age was similar, they were more likely to have been on dialysis for a shorter period of time with more residual renal function (Table 2). However, mean C-F and C-R PWV was not significantly different in subgroup A when compared to the other 13 patients. During dialysis in this subgroup, mean body weight fell by only 0.3±0.2 and 0.2±0.2 kg in the polysulphone and polyamide subgroups, respectively, and the mean arterial pressure fall was also minimal and comparable, being 2 mmHg in both groups (NS). In this group, mean aortic C-F PWV was significantly increased during dialysis with the polysulphone membrane, this effect being maximal 75 min after dialysis commencement (Figure 3) and representing a 40% increase ($P < 0.01$) compared to a 2% (NS) increase with the polyamide membrane. The post-dialysis polysulphone aortic PWV was still 21% higher 15 min after dialysis completion. A smaller but significant difference was noted at 15 min during C-R PWV monitoring in this subgroup ($P < 0.05$). A series of analyses of aortic C-F PWV in all 24 subjects, including subgroup A patients, during polysulphone dialysis,
Correlation between C-F PWV pre-dialysis and absolute difference of C-F PWV between pre-dialysis and at time 135 min during dialysis using the polysulphone membrane in subgroup A.

**Discussion**

Study patients represented a clinically stable haemodialysis population and included a wide age range as well as recently commenced and longer term patients. Medications such as anti-hypertensive agents were not stopped, not just for ethical reasons, but because the effects of dialysis and dialysis membranes should be evaluated in the routine clinical environment. However, subjects taking nitrates were excluded because of the profound effect of glyceryl trinitrate on vascular function and pulse pressure [8].

Polysulphone dialysis was associated with a significant relative increase in aortic C-F PWV when compared to the polyamide dialyser and suggest a relative increase in aortic stiffness with the polysulphone membrane rather than a reduction in aortic stiffness with the polyamide membrane. This is because of the mean fall in blood pressure during dialysis which occurred during both dialysis periods itself reduces PWV

$$\text{PWV} = \sqrt{\Delta P \times V / \Delta V \times p}$$

where $\Delta V$ and $\Delta P$ are changes in volume and pressure and $p$ is blood density. Because of the effects of changes in vascular volume and pressure on vascular function including PWV, a retrospective analysis of a subgroup where such changes were minimal was appropriate. This subgroup was clearly defined before analysis. The marked and persistent increase in aortic PWV during dialysis with the polysulphone dialyser in this group clearly demonstrates a profound acute effect of dialysis with this membrane on vascular function. The observation that in the same group of subjects under identical conditions, a polyamide membrane did not increase aortic PWV supports preliminary evidence that some dialysis membranes are less likely to interfere with vascular function [7]. It is difficult to attribute the relative lack of effect of the polyamide membrane on PWV when compared to polysulphone on physical forces since there were no significant differences between the dialysers in blood pressure change or fluid removal during dialysis or perfusion. Subjects were randomly allocated to either dialyser first and while ultrafiltration coefficients and molecular clearances were not measured, comparable results during the perfusion study make electrolyte and blood volume changes an unlikely cause of PWV differences and support the membrane bioincompatibility premise.

The relatively minor effect of dialysis membranes on the more muscular and less elastic subclavian-axillary-brachio-radial vessel (C-R) compared to the aorta (C-F) was not unexpected since diverse compensatory vascular mechanisms would be more likely to quickly buffer such changes, in contrast to the aorta where the polysulphone membrane changes were still present at 195 min (subgroup A). Due to the method used to measure the C-R, the Complior C-R PWV is artificially reduced.

**Pre-dialysis protocol**

In this group of nine subjects (five male; mean age 57 ± 18 years) where the respective dialysers were perfused with blood without dialysate, aortic C-F PWV was again significantly increased in the polysulphone group at 30 min ($P < 0.01$) with no significant change in the polyamide group (Figure 5). Mean blood pressure did not change during this procedure being, respectively, 101 ± 8 and 103 ± 8 mmHg pre-procedure, and 103 ± 8 and 102 ± 11 mmHg post-procedure. Furthermore, a significant negative correlation between pre-dialysis PWV and the increase in PWV during perfusion of the polysulphane dialyser was again noted ($r = 0.60; P < 0.01$).
The mechanisms of the observed polysulphone PWV changes remain speculative although several studies have reported increased cytokine production secondary to blood interactions with bioincompatible dialysis components [9], as well as reactive oxygen species and nitric oxide [10,11]. Cuprophone and cellulose membranes can stimulate bioincompatible responses [12,13] with oxidative stress commonly being attributed to the recurrent activation of polymorphonuclear neutrophils and monocytes during blood passage through dialysis circuits and subsequent generation of complement components following contact with bioincompatible membranes [14]. Apart from potential structural alterations, changes in vascular tone via endothelial release of nitric oxide and endothelin-1 can acutely alter arterial stiffness, even without a concomitant change in blood pressure [8]. Furthermore, polyamide membranes have recently been demonstrated to increase dimethylarginines, which are endogenous inhibitors of NO synthetase when compared to cellulose membranes [15]. A biocompatibility difference between similar synthetic membranes may relate to differences in hydrophilic/hydrophobic micro-domain structures with altered activation of the coagulation system. This is supported by markedly less in vitro generation of thrombin/antithrombin-III and platelet factor IV release with a polyamide membrane when compared to a polysulphone membrane [16]. Solute clearances during clinical haemodialysis with modern synthetic membranes significantly decrease with treatment time, a behaviour attributable to changes in membrane properties due to protein and/or cell deposition [16]. It is presumed that similar membrane changes explain the apparent improvement in PWV with the polysulphone membrane after 3 h of dialysis.

The negative correlation between the effect of the polysulphone membrane on aortic stiffness and pre-existing aortic stiffness suggests that the greater the degree of aortic disease, the less likely the vessel is to be damaged or functionally altered by a bioincompatible membrane. Consequently, patients with evidence of severe aortic disease as judged by prolonged PWV were relatively unaffected by dialysis. Evidence that the longer a patient had been on dialysis, the less the effect of polysulphone dialysis on vascular function is consistent with the above observation. Some but not all studies have also demonstrated a close association of atherosclerosis with length of time on dialysis [1,17,18]. The association of PWV with age in haemodialysis patients has previously been documented [6].

There are no studies comparable to ours. When radial artery pressure wave forms were measured pre- and post-dialysis, a profound effect of dialysis on aortic wave form characteristics was noted and hypothesized as improved vascular compliance due to altered vasoconstrictor/vasodilator balance [19]. However, different groups within the cohort responded in different ways, and pre-dialysis weight loss and blood pressure changes were large in all groups which would have profound effects on arterial function.

In a more recent study of endothelial function, aortic PWV (Complior) was again measured, pre- and post-dialysis, but not during dialysis [20]. Pre-dialysis PWV was similar to our results and PWV post-dialysis was not significantly increased by a polysulphone membrane supporting our observations.

In summary, this study demonstrated a direct effect of dialysis and haemoperfusion with a polysulphone membrane on vascular function supporting earlier indirect evidence of the adverse effects of dialysis membrane incompatibility in haemodialysis patients. Endothelial dysfunction and/or structural arterial changes are postulated to support the hypothesis that increased oxidative stress and its sequelae is a major contributor to increased atherosclerosis in this population [3]. This study also suggests that some membranes can be relatively biocompatible. The possible effects of brief but repeated adverse effects of incompatible dialysis membranes on arterial function, in particular the aorta, is of great concern since it may lead to endothelial degeneration. However, patients with relatively severe aortic disease may be less susceptible to the ill effects of membrane bioincompatibility, presumably because of existing endothelial degeneration. While repeated dialysis-induced endothelial damage is a proposed mechanism of long-term vascular damage, transient endothelial activation producing a period of brief arterial stiffening, possibly by reduced NO availability, may be an epiphenomenon without any significant long-term sequelae.

Acknowledgements. We thank Leanne Avis RN who supervised the dialysis and perfusion procedures. We also thank Gambro Pty Ltd for a grant-in-aid to complete the pre-dialysis perfusion studies. None of the authors have any other financial or personal associations with Fresenius Medical Care or Gambro Pty Ltd.

Conflict of interest statement. None declared.

References
8. Stokes GS, Ryan R. Can extended-release isosorbide mononitrate be used as adjunctive therapy for systolic hypertension? An open study employing pulse-wave analysis to determine effects of antihypertensive therapy. *Am J Geriatr Cardiol* 1997; 6: 11–19


Received for publication: 15.6.03
Accepted in revised form: 5.7.04