Short-Term Blood Pressure, Noradrenergic, and Vascular Effects of Nocturnal Home Hemodialysis

Christopher T. Chan, Paula J. Harvey, Peter Picton, Andreas Pierratos, Judith A. Miller, John S. Floras

Abstract—Long-term nocturnal hemodialysis, which uses longer and more frequent sessions than conventional hemodialysis, lowers clinic blood pressure and left ventricular mass. We tested the hypotheses that short-term nocturnal hemodialysis would (1) reduce ambulatory blood pressure; (2) cause peripheral vasodilation; (3) lower plasma norepinephrine concentration; and (4) improve the arterial response to reactive hyperemia (a marker of endothelium-dependent vasodilation). We studied 18 consecutive patients (age, 41±2; [mean±SEM]) before and 1 and 2 months after conversion from conventional (three 4-hour sessions per week) to nocturnal (six 8-hour sessions per week) hemodialysis. As the dialysis dose per session (Kt/V) increased from 1.24±0.06 to 2.04±0.08 after 2 months (P=0.02), symptomatic hypotension developed and most antihypertensive medications were withdrawn. Nocturnal hemodialysis nonetheless lowered 24-hour mean arterial pressure (from 102±3 to 90±2 mm Hg after 2 months; P=0.01), total peripheral resistance (from 1967±235 to 1499±191 dyne·s·cm⁻²; P<0.01) and plasma norepinephrine (from 2.66±0.4 to 1.96±0.2 nmol; P=0.04). Endothelium-dependent vasodilation could not be elicited during conventional hemodialysis (−2.7±1.8%) but was restored (+8.0±1.0%; P=0.001) after 2 months of nocturnal hemodialysis. The brachial artery response to nitroglycerin also improved (from 6.9±2.8 to 15.7±1.6%; P<0.05). Nocturnal hemodialysis had no effect on weight or on stroke volume. Rapid reversal of these markers of adverse cardiovascular events with more intense hemodialysis may translate into improved outcome in this high-risk group of patients. (Hypertension. 2003;42:925-931.)

Key Words: blood pressure ■ catecholamines ■ hemodynamics ■ hemodialysis ■ endothelium ■ muscle, smooth, vascular

Cardiovascular events are the leading cause of death in end-stage renal disease (ESRD).¹ In patients undergoing conventional hemodialysis (CHD), each of poor control of uremia,² hypertension,³ elevated catecholamines,⁴ activation of the renin-angiotensin-aldosterone axis,⁵ and impaired flow-mediated or endothelium-dependent vasodilation⁶ (EDV) has been linked to an increased likelihood of adverse cardiovascular events. Each of these risk factors is also associated with left ventricular (LV) hypertrophy and depressed LV systolic function, 2 additional markers of poor prognosis in the ESRD population.⁷,⁸ To date, CHD has not been shown to alter these cardiovascular risk factors. As a result, patients with ESRD still have a mortality rate of 22% per year.¹

Nocturnal hemodialysis (NHD), which provides 8 to 10 hours of renal replacement therapy during sleep, 5 to 7 nights per week, is a novel and more intense mode of dialysis.⁹ We recently reported a marked improvement in blood pressure (BP) control, a reduction in antihypertensive drug requirements, regression of left LV hypertrophy, and recovery of impaired LV systolic function after long-term (>2 years) NHD.¹⁰,¹¹ These adaptations occurred in the absence of any detectable reduction in extracellular fluid volume. How NHD might exert these effects independent of changes in volume status has not been established. Potential mechanisms include a fall in LV afterload resulting from decreased production or release or increased clearance, by dialysis of vasoconstrictor substances, improvement in endothelial function,¹⁰ or alterations in vascular smooth muscle cell responsiveness.¹²

In the present study, we tested the hypotheses that augmenting dialysis dose and frequency by NHD would over the short term: (1) reduce clinic and ambulatory blood pressure; (2) cause peripheral vasodilation; (3) lower plasma concentrations of norepinephrine and angiotensin II; and (4) improve flow-mediated vasodilation.

Methods

This protocol was approved by Research Ethics Boards of the Toronto General and Humber Regional Hospitals. After written informed consent was given, subjects were recruited from patients at these centers undergoing training before conversion from CHD to NHD. None had systolic dysfunction or any acute illness.

Protocol

Each subject was studied first while receiving CHD and again 1 and 2 months after conversion to a stable dose of NHD. All experiments

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were conducted in the morning, in the Toronto General Hospital Clinical Cardiovascular Physiology Laboratory. Baseline studies were performed ≥18 hours after conventional hemodialysis. To minimize circadian variation and replicate steady-state NHD conditions, subsequent experiments were performed ≥4 hours after the regular NHD session. All subjects abstained from tobacco and caffeine.

An 18-gauge peripheral venous cannula was inserted into an antecubital vein of the arm opposite to the vascular access. After 30 minutes of supine rest, blood was drawn to determine plasma norepinephrine (NE), renin activity (PRA), angiotensin II (AII), and aldosterone (aldo).13

Heart rate was measured continuously. Resting blood pressure was determined noninvasively in the arm opposite the arteriovenous fistula (Dinamap Pro 100, Critikon LLC). Stroke volume (SV) was estimated, using standard echo Doppler methods, as the product of the mean time-velocity integral of ascending aortic flow and the cross-sectional area of the aortic orifice.14 Total peripheral resistance (TPR) was derived from mean arterial BP and cardiac output (CO), the product of SV and heart rate (HR).

### Brachial Artery Vasodilation

Flow-mediated and endothelium-independent vasodilation (EIV) in the brachial artery of the arm opposite to that accessed for dialysis were quantified by studying responses to postischemic reactive hyperemia and sublingual nitroglycerin (GTN). The arterial diameter was imaged with a 7- to 10-MHz linear array transducer (B-mode ultrasound: UM9, Advanced Technology Laboratories). The arm and transducer were stabilized, and a longitudinal section of the artery was scanned 2 to 5 cm above the elbow. After the optimal image was secured, a baseline scan was recorded over a 20-second period. Postischemic reactive hyperemia was then induced in the forearm by inflating a BP cuff wrapped at least 5 cm below the antecubital fossa, to 50 mm Hg above systolic pressure, for 4.5 minutes. A second 2-minute scan was acquired, commencing 30 seconds before cuff deflation. Doppler flow measurements were obtained during the first resting scan and again during the first 15 seconds of reactive hyperemia. GTN (400 µg) was administered 10 minutes after hyperemia. Diameter and flow images were acquired 3 minutes later.

Images were recorded onto S-VHS videotape and onto a LabView-based (National Instruments) data acquisition software platform for subsequent analysis, with the use of a customized program that removed patient- and test-related information and grouped brachial artery images from different sessions and patients onto one randomized list to eliminate bias. With this method, the operator remained unaware of the study subject, time, or intervention until all analyses of these images were completed.

Mean arterial diameter was calculated across the segments selected by the operator. End-diastolic diameter was measured from trailing edge to leading edge of the blood-intima interface. Pixels were converted to millimeters by calibration against the real-time image. An average of 3 to 4 measurements was used to determine brachial artery diameter under each experimental condition. Blinded evaluation of 88 images obtained from 20 other subjects under a variety of experimental conditions resulted in a mean difference between 2 readings of 1.09%.

Arterial responses to hyperemia and GTN are expressed as the percent increase from baseline diameter. Blood flow was calculated as the product of the Doppler velocity integral, heart rate, and arterial cross-sectional diameter.

### Ambulatory Blood Pressure

On a nondialysis day before each study, noninvasive ambulatory BP monitoring (SpaceLabs 90210, SpaceLabs Medical Inc) was recorded from the arm opposite to that used for vascular access for dialysis every 15 minutes from 6 AM to 10 PM and every 30 minutes from 10 PM to 6 AM.

### Dialysis Prescriptions

Initially, each patient received conventional hemodialysis over a period of 4 hours, 3 times per week. Vascular access was achieved through either a long-term internal jugular catheter or an arteriovenous fistula. A dialysate flow rate of 500 to 750 mL per minute and F80 polysulfone dialyzers (Fresenius Medical Care) were used. After conversion to NHD, patients received NHD at home for 8 to 10 hours 6 nights per week through similar vascular access. A dialysate flow rate of 300 mL per minute and F80 polysulfone dialyzers or Polyflux-17 polyamide dialyzers (Gambro) were used. Predialysis and postdialysis weights and ultrafiltration rates were noted.

Dialysis dose per treatment was estimated by equilibrated Kt/V (eKt/V), as described by Daugirdas and colleagues,15 where eKt/V = spKt/V – 0.6(spKt/V)/t + 0.03 (spKt/V = single pool Kt/V, K = delivered clearance, t = dialysis time, and V = urea distribution volume). Single-pool Kt/V was determined by blood urea reduction ratio.16 Plasma phosphate concentration was measured monthly to estimate dialysis efficacy.

### Statistical Analysis

Data are presented as mean±SEM. Repeated-measures ANOVA was used to evaluate changes in variables over time. A 2-tailed probability value <0.05 was required for significance.

### Results

#### Conventional Hemodialysis

Eighteen consecutive CHD patients in training for NHD were recruited (Table 1). Their initial BP was well controlled by CHD and by concomitant drug therapy. The dose of CHD received and plasma phosphate concentrations attained conformed to current guidelines for dialysis adequacy17 (Table 2). Values for NE, PRA, AII, and aldosterone were all above their normal ranges.18

Hyperemia increased brachial artery flow 3-fold, but this stimulus had no effect on group mean values for brachial artery diameter (Table 2), indicating profound attenuation or absence of EDV when these patients were receiving CHD, despite concurrent therapy with agents known to increase EDV such as ACE inhibitors and angiotensin receptor antag-

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**Table 1. Patient Demographics (n=18)**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>41±2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F, n</td>
<td>11/7</td>
</tr>
<tr>
<td>Duration of dialysis (range), y</td>
<td>3.9±0.95 (0.11–17)</td>
</tr>
<tr>
<td>Etiology of ESRD, n</td>
<td></td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>7</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>4</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>3</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>3</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>3</td>
</tr>
<tr>
<td>Ethnicity, n</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
</tr>
<tr>
<td>African American</td>
<td>2</td>
</tr>
<tr>
<td>Comorbid conditions, n</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>11</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>2</td>
</tr>
</tbody>
</table>

ESRD indicates end-stage renal disease; IgA, immunoglobulin A.
onists. Dilator responses to GTN were present, but less than anticipated.

**Nocturnal Hemodialysis**

The sessional dialysis dose increased significantly with NHD (Table 2), as did the estimated weekly Kt/V (from 3.7±0.1 to 11.6±0.1, \( P<0.001 \)). Both clinic and ambulatory blood pressure fell progressively after conversion to NHD, and in the majority of patients, symptomatic hypotension developed. As a result, the treating nephrologists were obliged to reduce, on clinical grounds, and independent of the present investigations, the number of antihypertensive agents prescribed. Despite this withdrawal of (primarily vasodilator) hypotensive therapy, total peripheral resistance fell significantly. There were no differences in predialysis or postdialysis weights among the different sessions, indicating no significant reduction in extracellular volume with NHD. Moreover, stroke volume, an indirect marker of intravascular volume (preload), and heart rate were unchanged (Table 2 and Figure).

Plasma NE fell after 1 month of NHD and remained below CHD levels at the 2-month study (Figure). Plasma phosphate concentrations also decreased significantly after conversion to NHD (Table 2).

To ensure that hyperemia exerted a similar flow-mediated stimulus at each time point, the ratio of posthyperemic to prehyperemic blood flow was calculated for each subject at each experimental session. There was no difference in this estimate of brachial artery flow reserve with NHD (Table 2), indicating that a constant stimulus to flow-mediated, endothelium-dependent dilation was applied during each experimental session. Flow-mediated vasodilation, which was absent during CHD, was evident and significantly different from baseline values after 1 month of NHD. EDV increased

#### Table 2. Hemodynamics, Biochemistry, and Brachial Artery Responsiveness Before and After 1 and 2 Months of Nocturnal Hemodialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHD</th>
<th>1 Month of NHD</th>
<th>2 Months of NHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibrated Kt/V per session</td>
<td>1.24±0.06†</td>
<td>1.96±0.07†</td>
<td>2.04±0.09†</td>
</tr>
<tr>
<td>Plasma phosphate, mmol/L</td>
<td>1.91±0.2</td>
<td>1.22±0.09†</td>
<td>1.19±0.06†</td>
</tr>
<tr>
<td>Predialysis weight, kg</td>
<td>74.2±5.1</td>
<td>73.3±4.9</td>
<td>74.5±5.0</td>
</tr>
<tr>
<td>Postdialysis weight, kg</td>
<td>72.1±5.0</td>
<td>71.7±4.8</td>
<td>72.0±5.0</td>
</tr>
<tr>
<td>Ultrafiltration rate, L/h</td>
<td>0.60±0.1</td>
<td>0.35±0.04*</td>
<td>0.33±0.04*</td>
</tr>
<tr>
<td>24-h Systolic BP, mm Hg</td>
<td>135±5</td>
<td>125±3*</td>
<td>120±2*</td>
</tr>
<tr>
<td>24-h Diastolic BP, mm Hg</td>
<td>86±3</td>
<td>77±3*</td>
<td>75±2*</td>
</tr>
<tr>
<td>Resting systolic BP, mm Hg</td>
<td>140±5</td>
<td>124±3*</td>
<td>119±3*</td>
</tr>
<tr>
<td>Resting diastolic BP, mm Hg</td>
<td>82±3</td>
<td>75±3*</td>
<td>71±3*</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.9±0.4</td>
<td>5.3±0.4</td>
<td>5.5±0.5</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>63±5</td>
<td>64±5</td>
<td>68±6</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>78±3</td>
<td>75±3</td>
<td>80±4</td>
</tr>
<tr>
<td>Total peripheral resistance, dynes·s·cm⁻¹</td>
<td>1967±235</td>
<td>1647±185*</td>
<td>1499±191*</td>
</tr>
<tr>
<td>Norepinephrine, nmol/L</td>
<td>2.66±0.4</td>
<td>1.82±0.4*</td>
<td>1.91±0.2*</td>
</tr>
<tr>
<td>Plasma renin activity, ng·ml⁻¹·h⁻¹‡</td>
<td>4.6±1.1</td>
<td>1.7±0.4</td>
<td>4.4±0.9</td>
</tr>
<tr>
<td>Angiotensin II, pmol/L‡</td>
<td>11.2±2.7</td>
<td>17.5±6.5</td>
<td>16.5±4.2</td>
</tr>
<tr>
<td>Aldosterone, pmol/L‡</td>
<td>635±215</td>
<td>438±149</td>
<td>515±82</td>
</tr>
<tr>
<td>Antihypertensive medications (per patient)</td>
<td>2.5</td>
<td>0.6†</td>
<td>0.2†</td>
</tr>
<tr>
<td>ACEI, n</td>
<td>11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>ARB, n</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>β-blocker, n</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>α-blocker, n</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCB, n</td>
<td>14</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other vasodilators, n</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Brachial artery responses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change after hyperemia, %</td>
<td>-2.7±1.8</td>
<td>+4.7±1.7†</td>
<td>+8.0±1.0†</td>
</tr>
<tr>
<td>Change after GTN, %</td>
<td>6.9±2.8</td>
<td>8.8±1.4*</td>
<td>15.7±1.6*</td>
</tr>
<tr>
<td>Post-/pre-flow</td>
<td>3.01±0.2</td>
<td>3.1±0.3</td>
<td>3.5±0.2</td>
</tr>
</tbody>
</table>

Values are presented as mean±SEM or number, as indicated. CHD indicates conventional hemodialysis; NHD, nocturnal hemodialysis; Kt/V, dialysis dose; BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; post-/pre-flow, ratio of brachial artery blood flow between posthyperemia and prehyperemia maneuver; and GTN, nitroglycerin.

\*\( P<0.05 \) from values during CHD; †\( P<0.001 \) from values during CHD.

\( n=15 \).
further after the second month of therapy. In addition, NHD increased the vasodilator response to GTN from 6.9±2.8% (CHD) to 8.8±1.4% after 1 month and to 15.7±1.6% after 2 months (P<0.05).

To determine whether these responses to NHD were a function of the duration of dialysis, patients were divided into 2 subgroups, based on years on conventional hemodialysis (mean 1.7±0.3 versus 6.3±1.1 years). The magnitude of these principal adaptations to NHD (blood pressure, total peripheral resistance, drug withdrawals, plasma NE concentrations, and endothelium-dependent vasodilation) was similar (P≥0.5) between the 2 subgroups (data not shown).

**Discussion**

In ESRD patients receiving CHD, uremia, daytime and nocturnal hypertension, increased plasma norepinephrine concentrations, and impaired endothelium-dependent vasodilation are 4 independent risk factors for high cardiovascular mortality rates. Blunted vasodilator responses to either intracoronary infusion of nitroglycerin or brachial artery infusion of a nitric oxide donor are also potent predictors of cardiovascular events.\(^{19}\) Our study of ESRD patients representative of the North American self-care dialysis population appropriate for conversion to this novel mode of therapy\(^{20}\) shows for the first time that augmentation of dialysis dose and frequency by NHD can alter all of these markers of adverse cardiovascular events independent of the duration of prior renal replacement therapy. Significant reductions in blood pressure, total peripheral resistance, and plasma norepinephrine were achieved after only 1 month of NHD. Because antihypertensive therapy was withdrawn over this period and patients had well-controlled BP during CHD, these observations clearly underestimate the antihypertensive potential of this mode of dialysis.

When patients were receiving CHD, the brachial artery did not dilate in response to a 3-fold increase in local flow (rather, on average there was a 2.7±1.8% decrease in brachial artery diameter). However, after 2 months of NHD, flow-mediated
dilation was restored toward values described in healthy subjects of similar age. During CHD, responses to GTN were less than anticipated, but after a lag (Figure), EIV also increased, indicating that this normalization was due, in part, to improved smooth muscle responsiveness to endogenous nitric oxide. Importantly, these improvements in brachial artery vasodilation occurred in the context of withdrawal of pharmacologic modulators of the renin-angiotensin axis shown to enhance EDV.

More than 80% of ESRD patients have hypertension. Reflex neurogenic vasoconstriction, elicited by the failing kidney but not by changes in extracellular fluid volume, is considered an important component of this pathophysiology. Indeed, an inappropriate increase in peripheral resistance rather than cardiac output is the predominant hemodynamic abnormality in this population, in whom bilateral nephrectomy decreases mean arterial blood pressure by lowering total peripheral resistance.

Improved uremia control with longer periods of intermittent dialysis (6 to 8 hours per session) can lower blood pressure in the absence of any change in extracellular fluid volume, as considered an important component of this pathophysiology. Indeed, an inappropriate increase in peripheral resistance rather than cardiac output is the predominant hemodynamic abnormality in this population, in whom bilateral nephrectomy decreases mean arterial blood pressure by lowering total peripheral resistance.

Improved uremia control with longer periods of intermittent dialysis (6 to 8 hours per session) can lower blood pressure in the absence of any change in extracellular fluid volume, as assessed by bioimpedance, was not altered in these patients. In the present study, augmentation of dialysis dose and frequency by NHD resulted in a significant fall in total peripheral resistance despite withdrawal of vasodilator therapy, whereas stroke volume (an index of preload) and predialysis and postdialysis weights remained unchanged. Thus, the hypertensive response to NHD can be attributed to a decrease in the inappropriately elevated afterload of ESRD rather than to a fall in cardiac filling pressure or intravascular volume.

One factor contributing to the increase in peripheral resistance in ESRD is sympathetic nervous system activation. Because central sympathetic outflow to skeletal muscle is increased 2- to 3-fold in patients with native kidneys in situ but not after bilateral nephrectomy, sympathetic activation in ESRD has been attributed to a chemoexcitative reflex arising from the failing kidney. Indeed, hypertension in rats with chronic uremia after 5/6 nephrectomy can be prevented by renal afferent denervation. The renal R-receptor-mediated chemoreflex is dependent on excretory function and can be stimulated by tonic content of nondiuretic urine in the renal interstitium and renal ischemia and by ischemic metabolites such as adenosine. This reflex appears to persist, even after correction of systemic uremia by renal transplantation, unless all failed native kidneys are removed.

The present study is the first to demonstrate a sustained reduction in plasma norepinephrine with this more aggressive mode of hemodialysis. This observation is all the more remarkable when one considers that in the present series, ACE inhibition, an intervention reported to normalize sympathetic nerve discharge in chronic renal failure, was withdrawn in 10 of the subjects. If acute dialysis itself had any sympathoexcitatory aftereffects, these should have been greater during NHD than during the CHD phase of the study because of the shorter time from the end of the dialysis session. However, plasma norepinephrine concentrations were instead significantly lower after NHD. Whether this is due to the increased clearance of this neurotransmitter, by dialysis, or removal of a uremic stimulus to reflex neurogenic vasoconstriction cannot be determined from norepinephrine concentrations alone. However, if central sympathetic outflow to the heart and periphery is reduced by more intense hemodialysis, this action could account for the decrease in sympathetic modulation of nocturnal heart rate variability, the regression of LV hypertrophy, and the increase in ejection fraction of those ESRD patients with depressed systolic function documented in our previous studies of the long-term effect of NHD, in addition to the peripheral vasodilation documented in the present series. The absence of a parallel reduction in heart rate can be attributed to the withdrawal of β-blockade in all treated subjects (Table 1).

Mean values for PRA, angiotensin II, and aldosterone were unchanged, but these are all affected by withdrawal of ACE inhibitors, angiotensin receptor blockers, and β-adrenoceptor antagonists and in qualitatively different ways. We report these values, since venous blood was drawn for this purpose, but can derive no conclusions from them because of the confounding effect of unanticipated drug withdrawal.

Impaired endothelium-dependent, flow-mediated dilation has been linked to adverse cardiovascular outcomes. EDV in ESRD can be compromised by inflammation, the generation of reactive oxygen species, and increased sympathetic outflow to vascular beds. A decrease in endothelial nitric oxide bioavailability may also result from accumulation of uremic toxins. Acutely, EDV can be enhanced by a single session of CHD or by L-arginine administration. The present findings indicate that endothelium-dependent, flow-mediated vasodilation, which was markedly blunted or absent during CHD, can be restored by augmenting the dose and frequency of dialysis: NHD could achieve this effect by attenuating one or more of these pathophysiological mechanisms, as well as by augmenting the vascular smooth muscle response to endogenous nitric oxide. The time course of changes in EDV and EIV in the Figure suggests first that the latter mechanism must assume greater importance with further sessions of NHD, and, second, that the progressive fall in total peripheral resistance observed over this time period may result, in part, from a gradual reduction in vascular smooth muscle tone.

In healthy subjects, a 400-μg sublingual dose of GTN represents a maximal stimulus to smooth muscle vasodilation. Therefore, the progressive improvement in brachial artery dilation in response to GTN, in the present experiments, suggests that abnormalities of nitric oxide/soluble guanylate cyclase/cyclic GMP signaling or other contributors of smooth muscle tone also act to limit EIV in ESRD. This impairment could arise from hyperphosphatemia, increased osteopontin expression, elevated homocysteine, or other consequences of uremia. Importantly, this vascular pathology can be rectified if the dialysis frequency and dose are increased and serum phosphate is normalized. Because GTN can also augment endothelium-mediated dilation by increas-
increased nitric oxide synthesis or bioavailability, \(^\text{39}\) the restoration of flow-mediated dilation with NHD could also serve to increase the smooth muscle response to this pharmacological stimulus.

The principal limitation to the present study is the absence of a time-control group. However, all key outcome variables were acquired either blindly or objectively, to minimize bias, and their stability over a 1-month period, in the absence of interventions, has been previously documented. \(^\text{40}\)

**Perspectives**

NHD represents a novel mode of renal replacement therapy, with several potential clinical benefits. These include a reduction in blood pressure and the requirement for antihypertensive medications and augmented smooth muscle responsiveness to GTN. Indeed, over the short term, patients with ESRD who are prescribed nitrates for angina may have greater symptom relief as a result of this increased vasodilator responsiveness.

Thus far, most cardiovascular risk factors specific to renal failure have not been countered by CHD therapy. The result is a high annual cardiovascular mortality rate as compared with the non-ESRD population. \(^\text{1}\) Increasing thrice-weekly K/V with CHD from 1.16 ± 0.08 to 1.53 ± 0.09 has had no effect in cardiovascular outcomes. \(^\text{41}\) By contrast, NHD in the present series increased equilibrated K/V from 1.24 ± 0.06 to 2.04 ± 0.09 per session (and from 3.7 ± 0.1 to 11.6 ± 0.1 per week). Potentially beneficial effects on blood pressure, adrenergic drive, and endothelial tone were detected after only 1 month of therapy. If sustained over a longer time period, the rapid reduction in these several potent predictors of adverse cardiovascular events achieved with more intense hemodialysis may translate into improved cardiovascular event rates in this highly vulnerable population.

**Acknowledgments**

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**References**


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