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Nocturnal hemodialysis increases arterial baroreflex sensitivity and compliance and normalizes blood pressure of hypertensive patients with end-stage renal disease

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Nocturnal hemodialysis increases arterial baroreflex sensitivity and compliance and normalizes blood pressure of hypertensive patients with end-stage renal disease.

Background. Impaired neural control of heart rate, elevated arterial stiffness, and hypertension place patients with end-stage renal disease (ESRD) at increased risk of cardiovascular mortality. Nocturnal hemodialysis (6 × 8 hours/week), a more intense program than conventional hemodialysis (3 × 4 hours/week), lowers blood pressure and restores brachial dilator responses to hyperemia and nitrates.

Methods. We hypothesized that nocturnal hemodialysis would increase arterial baroreflex sensitivity for heart rate of hypertensive ESRD patients by an afferent vascular mechanism. Ten consecutive hypertensive ESRD patients (age 42 ± 4) (mean ± SEM) receiving conventional hemodialysis were studied before and 2 months after conversion to nocturnal hemodialysis. Regression slopes relating RR interval responses to rises or falls in systolic blood pressure were averaged to derive spontaneous baroreflex sensitivity for heart rate for each patient, and the stroke volume/pulse pressure ratio was used to estimate total arterial compliance.

Results. Dialysis dose (Kt/V per session) increased from 1.2 ± 0.05 to 2.1 ± 0.1 ($P < 0.05$). Despite withdrawal of antihypertensive medications (from 2.9 to 0.1 drugs/patient), nocturnal hemodialysis lowered systolic blood pressure (from 143 ± 4 to 120 ± 6 mm Hg) ($P = 0.001$). Both baroreflex sensitivity (from 4.76 ± 1.1 msec/mm Hg to 6.91 ± 1.1 msec/mm Hg) ($P = 0.04$) and total arterial compliance (from 0.98 ± 0.13 mL/mm Hg to 1.43 ± 0.2 mL/mm Hg) ($P = 0.02$) were higher following conversion to nocturnal hemodialysis. Increases in baroreflex sensitivity correlated with increases in stroke volume/pulse pressure ($r = 0.845$, $P = 0.002$).

Conclusion. These findings are consistent with the concept that nocturnal hemodialysis increases baroreflex sensitivity via greater afferent baroreceptor responsiveness to pulsatile pressure. A more favorable risk profile, due to enhanced baroreflex regulation of the circulation and vascular compliance, may translate into lower cardiovascular event rates in ESRD patients receiving nocturnal hemodialysis.

Key words: nocturnal home hemodialysis, baroreflex sensitivity, arterial compliance, blood pressure.

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Altered neural regulation of the heart and circulation [1, 2], elevated arterial stiffness, [3] and hypertension [4] are common in end-stage renal disease (ESRD). Each of these factors contributes to the high cardiovascular event rate of patients with this condition. A regulatory mechanism impaired by all three abnormalities is the arterial baroreflex, the principal short-term regulator of heart rate and blood pressure.

Mechanoreceptor nerve endings, situated in the carotid sinus and aortic arch, discharge when stretched during systole, informing the nucleus tractus solitarii, via the glossopharyngeal and vagal afferent nerves, respectively, of changes in systolic blood pressure [5, 6]. The reflex heart rate response to baroreceptor stimulation is effected through efferent vagal nerve activation and sympathetic neural withdrawal. The gain of the arterial baroreflex for heart rate (arterial baroflex sensitivity) can be determined, in conscious humans, from the slope of the relationship between changes in systolic blood pressure (stimulus) and changes in pulse interval (response) following bolus injection or infusion of vasoactive drugs [7, 8], or over the course of spontaneous rises and falls in arterial blood pressure [9, 10]. These rapid (i.e., within seconds) heart rate responses are mediated primarily through changes in efferent vagal discharge [10].

A reduction in baroreceptor nerve firing in response to changes in systolic or pulse pressure [5, 11], whether due to decreased conduit artery compliance, diminished endothelial prostacylin production, or increased local free radial generation [12–15] contributes to the attenuated arterial baroreflex gain that occurs with age, with increasing blood pressure [8, 16, 17], or in disorders of arterial elastin fiber assembly [18]. A reduction in arterial baroflex sensitivity has important clinical consequences. In cross-sectional studies involving patients with high

normal and elevated blood pressure, arterial baroflex sensitivity related inversely to blood pressure variability at rest [19], and in response to mental stress and exercise [8]. In prospective studies of patients following myocardial infarction or with heart failure, a decrease in both reflex and tonic vagal heart rate modulation predicted greater cardiovascular and total mortality [20–23].

In ESRD, both reflex heart rate responses to increases or decreases in blood pressure induced by phenylephrine, angiotensin, or amyl nitrate [24–26], and spontaneous arterial baroflex sensitivity [27] are markedly attenuated. Pulse interval responses to phenylephrine, prior to the initiation of dialysis, are less than 50% of that predicted on the basis of patients' ages and blood pressures, owing to reduced vagal and augmented efferent sympathetic modulation of heart rate [26]. This profound reduction in arterial baroflex sensitivity gain is clearly reversible, since normal, or near-normal values for arterial baroreflex sensitivity have been found in renal transplant patients [27, 28]. However, arterial baroreflex sensitivity is not affected by acute or short-term (4 to 10 weeks) conventional hemodialysis, and increases only modestly with long-term conventional hemodialysis [25, 28].

Within 1 to 2 months of its initiation, nocturnal hemodialysis, at a higher dialysis dose and with more frequent application than conventional hemodialysis, lowers blood pressure, peripheral resistance, plasma norepinephrine concentration, and plasma phosphate, and restores brachial artery responsiveness to both endogenous (hyperemia) and exogenous nitric oxide (nitroglycerin) [29]. Nitric oxide increases brachial artery elasticity [30]. If nocturnal hemodialysis improved the distensibility of conduit, as well as muscular arteries, leading to an increase in aortic arch and carotid sinus compliance, baroreceptor discharge responsiveness to pulsatile pressure should be augmented, resulting in greater reflex vagal modulation of heart rate. Although an attractive concept, tests of this hypothesis have yet to be reported. Indeed, several drugs used to treat hypertension have been shown to either increase arterial compliance, or augment arterial baroreflex sensitivity, but concurrent changes in these two variables with therapy have yet to be correlated.

Our objectives in the present study were first, to test the hypothesis that reductions in blood pressure following conversion from conventional hemodialysis to nocturnal hemodialysis would be accompanied by an increase in arterial baroreflex sensitivity, and second to determine whether any increase could be attributed to an afferent mechanism (i.e., greater arterial compliance). For this latter purpose, we determined the effect of nocturnal hemodialysis on the ratio of stroke volume:pulse pressure, a well-established noninvasive estimate of total arterial compliance [31–38].

METHODS

Subjects

We studied ten consecutive hypertensive ESRD patients [five men, mean age 42 ± 4 years (mean ± SE)] in training for nocturnal hemodialysis. All had received conventional hemodialysis for at least 2 years. Their ESRD was due to glomerulonephritis ($N = 4$), hypertensive nephrosclerosis ($N = 2$), polycystic kidney disease ($N = 2$), or vasculitis ($N = 2$). None had documented left ventricular systolic dysfunction or any acute illness at the time of study. The present protocol is one aspect of a larger investigation of nocturnal hemodialysis approved by the Research Ethics Boards of the Toronto General and Humber Regional Hospitals of the University of Toronto.

Protocol

Each subject was studied first while receiving conventional hemodialysis and again 2 months after a stable dose of nocturnal hemodialysis. All experiments 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 nocturnal hemodialysis conditions, subsequent experiments were performed ≥4 hours after the regular nocturnal hemodialysis session. All subjects abstained from tobacco and caffeine.

Lead II of the electrocardiogram (ECG) rate was measured to derive a continuous measure of heart rate. Resting blood pressure was determined noninvasively in the arm opposite the arteriovenous fistula (Dinamap Pro 100) (Critikon LLC, Tampa, FL, USA). Stroke volume 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 [39]. Total peripheral resistance (TPR) was derived from mean arterial blood pressure and cardiac output (CO), the product of stroke volume and heart rate. For each patient, the ratio of stroke volume to pulse pressure was derived, as an estimate of total arterial compliance [37].

Arterial baroreflex sensitivity for heart rate

Arterial baroreflex sensitivity for heart rate was calculated using the sequence method, as described previously in detail [9]. In brief, the ECG signal was digitized at 1000 Hz. Sequences of three or more cardiac cycles during which the systolic blood pressure and the R-R interval of the subsequent beat either rose or fell in parallel were identified. For each sequences, changes in R-R intervals were related to the antecedent changes in systolic blood pressure by least-squares linear regression analyses. The

Table 1. Dialsyis dose, hemodynamics, baroreflex sensitivity for heart rate, and medication requirements before and after 2 months of nocturnal hemodialysis

Variables	Conventional hemodialysis	2 months of nocturnal hemodialysis	*P* value
Kt/V per session	1.2 ± 0.05	2.1 ± 0.1	0.008
Phosphate *mmol/L*	2.01 ± 0.3	1.29 ± 0.11	0.04
Systolic blood pressure *mm Hg*	143 ± 4	120 ± 6	0.001
Diastolic blood pressure *mm Hg*	86 ± 5	70 ± 5	0.02
Pulse pressure *mm Hg*	56 ± 3	49 ± 2	0.05
Heart rate min^{-1}	76 ± 7	77 ± 1	0.93
Stroke volume *mL*	55 ± 7	66 ± 9	0.07
Weight *kg*	64.1 ± 11.9	64.2 ± 11.7	0.70
Stroke volume/pulse pressure *mL/mm Hg*	0.98 ± 0.13	1.43 ± 0.2	0.019
Baroflex sensitivity *msec/mm Hg*	4.76 ± 1.1	6.91 ± 1.1	0.04
Medications	2.9	0.1	<0.001
Angiotensin-converting enzyme inhibitors *number*	5	0	
Angiotensin receptor blocker number	1	0	
β blocker *number*	3	1	
α blocker *number*	2	0	
Calcium channel blocker *number*	6	0	
Other vasodilators *number*	1	0	

$N = 10$. Values are presented as mean ± SEM or number, as indicated.

mean value for those slopes with highly correlated sequences ($r > 0.85$) was derived to represent spontaneous arterial baroreflex sensitivity for heart rate for each subject. A minimum of three such slopes at each study session, as confirmed by visual inspection, was required for such determination.

Dialysis prescriptions

Conventional hemodialysis was administered over 4 hours, 3 times per week, via 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, Lexington, MA, USA) were used. After conversion to nocturnal hemodialysis, patients received nocturnal hemodialysis 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 of Polyflux-17 polyamide dialyzers (Gambro, Hechnigen, Germany) 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 et al [40]:

$$\mathrm{eKt/(eKt/V} = \mathrm{spKt/V} - 0.6(\mathrm{spKt/V})/\mathrm{t} + 0.03$$

where spKt/V is single pool Kt/V, K is delivered clearance, t is dialysis time, and V is urea distribution volume. Single-pool Kt/V was determined by blood urea reduction ratio. Plasma phosphate concentration was measured monthly to estimate dialysis efficacy.

Statistical analysis

Data are presented as mean ± SEM. Student *t* test for paired variables was used to evaluate changes related to dialysis. A two-tailed probability of $P < 0.05$ was required for significance.

RESULTS

Baseline characteristics

The initial blood pressure of these ten hypertensive conventional hemodialysis patients in training was well controlled by the combination of dialysis and drug therapy. The dose of conventional hemodialysis received and the plasma phosphate concentration obtained conformed to current dialysis guidelines [41] (Table 1).

Nocturnal hemodialysis

The dialysis dose received (Kt/V per session) increased significantly after conversion to nocturnal hemodialysis (from 1.2 ± 0.05 to 2.1 ± 0.1) ($P < 0.05$) (Table 1). In addition, the frequency of dialysis doubled. Blood pressure fell, by 23/16 mm Hg (Table 1). Because symptomatic hypotension developed in the majority of patients, the treating nephrologists were obliged to reduce, on clinical grounds, and independent of the present investigations, the number of antihypertensive agents prescribed (from 2.9 to 0.1 drugs per patient) ($P < 0.001$). Thus, the true antihypertensive impact of nocturnal hemodialysis may actually have been much greater.

Mean heart rate was unaffected by mode of dialysis (Table 1), whereas arterial baroflex sensitivity increased from 4.76 ± 1.1 to 6.91 ± 1.1 (msec/mm Hg) ($P < 0.04$) following conversion from conventional hemodialysis to nocturnal hemodialysis. Over the same time period, the stroke volume/pulse pressure ratio also rose, from 0.98 ± 0.13 to 1.43 ± 0.2 mL/mm Hg ($P = 0.019$) (Table 1). There was a positive correlation between these changes

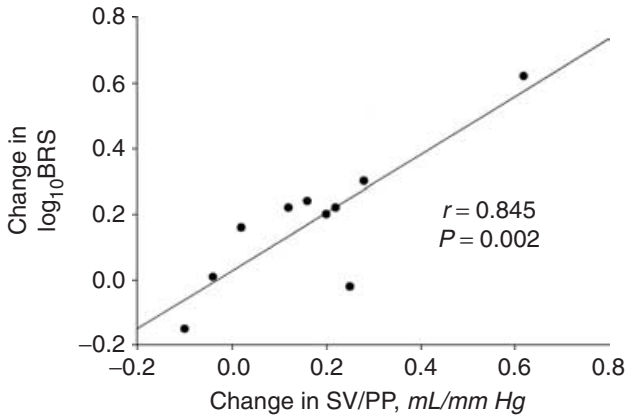

Fig. 1. Significant positive relationship between changes in stroke volume/pulse pressure ratio (SV/PP) and changes in baroreflex sensitivity for heart rate (BRS) 2 months after conversion from conventional to nocturnal hemodialysis.

in stroke volume/pulse pressure and $\log_{10}$ arterial baroreflex sensitivity ($r = 0.845$, $P = 0.002$) (Fig. 1).

DISCUSSION

We have previously shown that chronic nocturnal hemodialysis lowers the total peripheral resistance and systemic arterial pressure of ESRD patients converted from conventional hemodialysis and restores brachial artery dilator responses to flow-mediated dilation and nitroglycerin [29]. We now report three novel, additional, effects of nocturnal hemodialysis: (*1*) a significant increase in heart rate modulation by the arterial baroreflex; (*2*) a significant increase in estimated total arterial compliance; and (*3*) a significant positive correlation between changes in these two variables resulting from this intervention. Augmentation of arterial baroreflex sensitivity in the present study occurred in the absence of any change in resting heart rate, indicating, in addition to this increase in gain, adaptation, or resetting, of the baroreceptor-heart rate reflex to the lower prevailing blood pressure during nocturnal hemodialysis.

In contrast, Pickering, Gribbin, and Oliver [25] did not detect any significant increase in arterial baroreflex slopes generated by phenylephrine injection after acute reductions in blood pressure resulting from single dialysis sessions, and, 2 to 3 months of conventional hemodialysis have little or no effect on arterial baroreflex sensitivity [25, 28]. Thus, neither hypotension per se nor intermittent dialysis is sufficient to improve arterial baroreflex sensitivity in ESRD patients; longer-term functional or structural changes, not obtained with conventional hemodialysis, may be required.

The spontaneous sequence method yields values highly correlated to those obtained following bolus administration of phenylephrine and sodium nitroprusside [10]. In a study of 61 unmedicated patients with high or high normal blood pressure, in whom arterial blood pressure was measured directly, and blood pressure elevated acutely by intravenous doses of phenylephrine, the independent effects of these two variables on arterial baroreflex sensitivity could be expressed by the regression equation [8]:

$$\log_{10}\text{ arterial baroreflex sensitivity} = 1.943 - [(0.00445) \times (\text{systolic blood pressure}) - (0.01059) \times (\text{age})]$$

Entering the values obtained in the present study into this equation would yield an expected arterial baroreflex sensitivity during conventional hemodialysis of 7.27 msec/mm Hg, and an expected arterial baroflex sensitivity during nocturnal hemodialysis of 9.29 msec/mm Hg (i.e., a 28% increase).

Importantly, the observed gain of the baroreceptor-heart rate reflex while these ESRD patients were receiving conventional hemodialysis was substantially lower, and its 45% increase 2 months after conversion to nocturnal hemodialysis much greater than would be anticipated simply on the basis of age and systolic blood pressure [8]. Moreover, this augmentation occurred in the setting of withdrawal of angiotensin-converting enzyme (ACE) inhibitors, β adrenoceptor antagonists, and angiotensin receptor blockers. Because each of these drug classes has been shown to improve arterial baroreflex sensitivity [19, 35, 42, 43], and ACE inhibitors have been shown to decrease pulse wave velocity (i.e., increase compliance) in hemodialysis patients [44], an even greater increase in both arterial baroreflex sensitivity and arterial compliance might have been anticipated, had these antihypertensives been continued up until the time of the nocturnal hemodialysis study.

The present findings are consistent with the concept that one or more mechanisms, specific to chronic renal failure, and modifiable by nocturnal hemodialysis, act to attenuate the baroreceptor-heart rate reflex at one or more peripheral or central sites. Of note, in experimental chronic renal hypertension, central integration of baroreceptor input is also impaired [45]. Angiotensin II, which acts centrally to blunt efferent vagal discharge, and increase sympathetic nerve firing [46], is an obvious candidate, but its plasma concentrations have not been shown to fall after conversion to nocturnal hemodialysis [29]. Less neural release of the vasoconstrictor norepinephrine cannot explain these findings, because application of α adrenoceptor agonists to the carotid sinus increases, rather than decreases baroreceptor nerve firing rates [47]. The possibility of lower oxidative stress is suggested by a report that ascorbic acid infusion increases the arterial baroreflex sensitivity of healthy elderly men [14].

Our prior observation that conversion from conventional hemodialysis to nocturnal hemodialysis not only led to a significant reductions in peripheral resistance, but also improved both endothelium-dependent and endothelium-independent vasodilation of a muscular artery, and normalized normal plasma phosphate concentrations [29], led us to propose the concept that nocturnal hemodialysis induces, over time, structural (e.g., arterial decalcification) or functional vascular changes (e.g., an increase in the bioavailability of endothelial-derived nitric oxide [30]), resulting in a decrease in the stiffness of conduit arteries, the site of arterial baroreceptor afferent nerve endings. If so, such changes would be anticipated to improve baroreceptor nerve firing properties [12].

Distensibility of the arterial tree in humans has been estimated in a variety of ways, from pressure volume curves using postmortem arteries [48], to vascular ultrasound [49–51], measures of pulse wave velocity [52], and in vivo studies involving magnetic resonance imaging [53]. The noninvasive method applied in the present study, based upon the ratio of Doppler-derived left ventricular stroke volume to brachial artery pulse pressure, has been applied by a number of groups to estimate total arterial compliance in both cross-sectional and longitudinal studies [32–38]. This ratio correlates well with values obtained by invasive determination of pulse wave velocity [31], and was recently shown to predict coronary heart disease mortality in a population of elderly men [38].

Increased arterial stiffness, whether manifested as an increase in arterial pulse wave velocity, aortic augmentation index, or the pulse pressure/stroke volume ratio, is a feature common to ESRD patients receiving conventional hemodialysis [54–57] and one that relates strongly to their all-cause mortality [3]. In the absence of concurrent improvement in arterial compliance, blood pressure reduction per se, does not alter these cardiovascular event rates [58]. Greater arterial stiffness in ESRD has been attributed to the presence of both structural and dynamic factors, including uremia; fluid overload, hypertension; increased tissue and circulating vasoconstrictors; less nitric oxide synthesis, or bioavailability, leading to endothelial dysfunction; and poorly controlled hyperparathyroidism promoting arterial calcification [44, 55, 56, 59–61]. Conversely, an improvement in phosphate balance, or an increase in nitric oxide synthesis or bioavailability, as demonstrated in our previous report [29], should result in greater arterial compliance. Importantly, nocturnal hemodialysis, unlike conventional hemodialysis, reverses many of the abnormalities of ESRD [29, 62, 63].

Normalization of vascular volume by nocturnal hemodialysis might also improve arterial compliance, but any such effect is likely too modest to account for the present findings. Hemodialysis to dry weight does not result in any acute change in pulse wave velocity [44] or carotid distensibility [64] unless performed in the presence of ACE inhibition [44]. By contrast, in the present series, an increase in arterial compliance was evident despite withdrawal of ACE inhibitors, weights postdialysis were similar on study mornings after conventional hemodialysis and nocturnal hemodialysis (Table 1), and the hypotensive effect of conversion from conventional hemodialysis to nocturnal hemodialysis resulted from decreases in afterload (total peripheral resistance) rather than preload (stroke volume) [29].

Improved conduit artery compliance after conversion to nocturnal hemodialysis should result in greater mechanoreceptor stretch and afferent nerve firing in response to the same distending pressure. Indeed, Kingwell et al [49] found stiffness of the transverse aortic arch to be an important determinant of baroreflex-mediated responses to phenylephrine and nitroprusside in normotensive and hypertensive men, and in a subsequent series of experiments in young and older healthy sedentary and endurance trained men, Monahan et al [50, 51] found that arterial baroflex sensitivity tracked changes in carotid artery diameter in response to changes in blood pressure.

Our hypothesis that nocturnal hemodialysis would increase arterial baroreflex sensitivity by an afferent mechanism (i.e., a reduction in conduit artery stiffness), was supported by two key observations, namely an increase in the stroke volume/pulse pressure ratio from 0.98 $\pm$ 0.13 mL/mm Hg to 1.43 $\pm$ 0.2 mL/mmHg, a finding consistent with greater total arterial compliance during nocturnal hemodialysis than conventional hemodialysis, and a significant positive correlation between increases in the stroke volume/pulse pressure ratio, and increases in arterial baroflex sensitivity (Fig. 1). Importantly, a correlation between such changes, as a result of either pharmacologic or nonpharmacologic treatment of hypertension, has not been reported previously.

CONCLUSION

Two months after the frequency, duration, and dose of dialysis were increased in these hypertensive ESRD patients, by conversion from conventional hemodialysis to nocturnal hemodialysis, there was a substantial fall in blood pressure and an increase in the arterial baroreflex regulation of heart rate. A parallel increase total arterial compliance, and a significant positive relationship between changes in these two variables, is consistent with the concept that this augmented reflex vagal heart rate modulation results from greater afferent baroreceptor responsiveness to pulsatile pressure. Future investigations would benefit from specific assessment of carotid sinus and aortic arch compliance, and the possibility that conversion of these ESRD patients from conventional hemodialysis to nocturnal hemodialysis augmented arterial baroreflex sensitivity through additional central or

efferent mechanisms, affected beneficially by increased uremia clearance, should also be considered.

Greater arterial compliance and more potent baroreflex modulation of both heart rate and sympathetic outflow have several potential cardiovascular benefits, including lower blood pressure [42] and pulse pressure, improved ventricular arterial coupling [65], leading to regression of left ventricular hypertrophy [66], more potent damping of blood pressure variability [8], and a reduction in the probability of sudden cardiovascular death [67]. Indeed, pharmacologic interventions shown to increase arterial baroreflex sensitivity [19, 35, 42, 43] also improve survival rates following myocardial infarction, or in heart failure [68–71]. Thus, the augmented neural regulation of heart rate, the increase in the stroke volume/pulse pressure ratio and the lower blood pressure modify the cardiovascular risk profile of these ESRD patients. Over time, these changes following conversion to nocturnal hemodialysis may translate into lower cardiovascular event rates in this high-risk population.

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