Vasomotion of Renal Blood Flow in Essential Hypertension
Oscillations in Xenon Transit
NORMAN K. HOLLENBERG AND TAMAS SANDOR

SUMMARY To assess the frequency and magnitude of phasic renal blood flow changes in essential hypertension, we applied an analytical method based on the estimation of power spectral density to xenon transit through the kidney. Despite similar age and gender distribution of the patients and exclusion of those with accelerated hypertension, mean renal blood flow was significantly lower in 100 patients with essential hypertension (299 ± 8 ml/100 g/min) than in the 144 normal subjects (335 ± 6 ml/100 g/min; p < 0.001). Normalized power, the index of oscillatory behavior, was more than twice normal in patients with essential hypertension (p < 0.001), but there was no difference in the frequency or cycle length of the oscillation. Two maneuvers that induced renal vasoconstriction, the application of cuffs to the thighs which were then inflated to diastolic blood pressure and an emotional provocation, reduced renal blood flow much more in patients with essential hypertension (p < 0.01) in association with a striking increase in normalized power (p < 0.001). The oscillations, which reflected not the phasic blood pressure change but rather the phasic change in renal perfusion, provided additional evidence that renal vasoconstriction plays an active role in the pathogenesis of essential hypertension. (Hypertension 6: 579-585, 1984)

KEY WORDS • renal vascular reactivity • reflex renal responses • renin-angiotensin system • plasma catecholamines

Oscillatory behavior has been widely documented in biology, particularly in the cardiovascular system. In smooth muscle, slow oscillatory electrical potential changes have been found that appear to reflect pacemaker activity for myogenic rhythms. This phenomenon, previously well documented for nonvascular smooth muscle, has led to speculation concerning a similar mechanism and pacemaker activity in vascular smooth muscle.

Multiple observations suggest that renal vasoconstriction may be responsible for the reduced renal perfusion in most patients with uncomplicated essential hypertension. Sequential determinations of blood flow have revealed larger variations in flow than those that occur in normal subjects. The renal vasculature shows a potentiated blood flow response to a wide variety of vasodilator agents, and the potentiated flow response is often associated with a striking reversal of the abnormalities seen in the renal arteriogram.

While there is moment-to-moment variation in renal perfusion in patients with essential hypertension, the design of earlier studies did not allow identification of periodic behavior.

Some years ago we observed a qualitative abnormality in the character of xenon transit through the kidney, with a striking short-term variation in the washout of xenon in patients with hepatic cirrhosis. During a survey of the transit of radioxenon through the human kidney, we discovered that low amplitude oscillations were often present in the data derived from patients with essential hypertension. To study this oscillatory behavior, we applied an analytical method, based on the estimation of the power spectral density, to xenon transit through the human kidney. The analysis demonstrates an oscillatory abnormality in many patients with essential hypertension and provides evidence that favors a role for reflex activation in its genesis.

Methods

Subjects
We studied 144 normal subjects and 100 patients with essential hypertension with techniques we have described in detail. All subjects were admitted to the metabolic ward where a thorough evaluation ruled out significant cardiovascular, adrenal, or intrinsic renal disease in the normal subjects. Essential hypertension was established on the basis of a detailed eval-
uation to rule out the presence of significant secondary causes. Patients with azotemia were excluded from the analysis.

All patients underwent renal arteriography because of the usual clinical indications; and normal subjects, because they were being assessed as potential kidney donors. In the patients with essential hypertension, the indication was often an unusually early onset of hypertension or a difference in the size of the kidneys as demonstrated by intravenous pyelography or radiohippuran renography.

Transit of xenon through the kidney was assessed by injection of about 0.4 ml of saline solution saturated with xenon as a bolus. The injection was followed with a 1.4 ml flush; dead space of the catheter system was less than 1.0 ml. The transit of the xenon through the kidney was monitored by a probe-mounted scintillation detector with a 3-inch cylindrical collimator oriented so as to minimize the volume of lung in the field. The peak counts in the first study always exceeded 2000 cps and exceeded background by a factor of at least 300. When a second study was performed, the count rate always exceeded 5000 cps and exceeded background by a factor of 200. A second matched scintillation detector was placed over the head, thigh, or contralateral kidney to identify any possible contribution due to recirculation of xenon. Only minor recirculation occurred, and it was never periodic nor did it correlate with the oscillations in renal transit.

The transit of xenon was followed for over 3 minutes in each case, at which time the radioactivity had fallen to less than 5% of peak. Repeat determinations were routinely delayed until the radioactivity had fallen to less than 3% of peak, which rarely took more than 10 minutes. The arterial catheter was also routinely used to enable continuous measurements of arterial blood pressure with a pressure transducer (Model P23Dc, Statham Gould Transducer, Oxnard, California) and a multichannel recorder (Electronics for Medicine, Honeywell, Medical Electronics Division, Pleasantville, New York). The electrocardiogram and beat-to-beat heart rate changes were also monitored continuously with a cardiotachometer (Electronics for Medicine).

In 17 patients with essential hypertension and 12 normal subjects, the flow determinations were repeated to assess the stability of the indices we used in the absence of an obvious stimulus to a change in renal perfusion. To induce a reflex response to a physiological stimulus, blood pressure cuffs were applied to the upper thigh and inflated to diastolic pressure for periods of up to 15 minutes in 15 normal subjects and in 15 patients with essential hypertension. A fall in blood pressure did not occur in any subject in response to this stimulus.

To induce an emotional response, we employed Raven's Progressive Matrices, a nonverbal I.Q. test, in 21 normal subjects and in 15 patients with essential hypertension. The stressful stimulus arose from attempts at answering difficult questions in a limited, generally inadequate time interval.

Analytic Method

The counts were recorded every 2 seconds during the first minute and every 6 seconds throughout the remaining part of the studies. It was assumed that the counts could be fitted by a biexponential function of the form

$$g(t) = A_1 \exp(-\alpha_1 t) + A_2 \exp(-\alpha_2 t)$$

where $g(t)$ denotes counts as a function of time; $A_1$, $A_2$ are the amplitudes; and $\alpha_1$, $\alpha_2$ are the decay constants of the respective exponential components. Based on the maximum likelihood principle, a computer algorithm was developed to determine the "best" values of the above parameters and their statistical errors. As described below, the counts in most subjects revealed significant sinusoidal variations, which were superimposed on the washout curves. The properties of the superimposed signals were analyzed by estimating their power spectral density, which described the frequency decomposition of the average power. The average power $P_{AV}$, of the mean square value of a signal, $S$, sampled at $M$ points is defined as:

$$P_{AV} = \frac{1}{M} \sum_{r=1}^{M} S_r^2$$

A convenient measure of the average power is the mean square value of $S$, about the mean: this index is identical to the variance. In our case, this quantity is the difference between the counts in every time interval, $y_t$, and the line of best fit defined by Equation 1. To have a common unit of measurement we introduced a normalization procedure in the computation of average power. This index, termed "normalized power," can be written for a selected patient's data as:

$$P_{AV} = \frac{1}{N} \sum_{t=0}^{N-1} (y_t - g_t)^2/g_t = \frac{1}{N} \sum_{t=0}^{N-1} x_t^2$$

where $x_t = (y_t - g_t)/\sqrt{g_t}$ is the normalized signal, and $N$ is the number of sampled data in the washout curve. Normalization of the data is equivalent to a scaling of the difference signal $(y_t - g_t)$ by the standard deviation, which is $Vg_t$ for counts that obey Poisson distribution.

Most signals that occur in practice can be approximated by means of suitably chosen periodic functions. We employed Fourier analysis, where these are sine and cosine functions. By computing the estimate of the power spectral density $S_n(\omega)$, the average signal power can be decomposed into contributions from the sine and cosine functions, termed "harmonics." It can be shown that

$$S_n(\omega) = \frac{1}{N} \sum_{n=0}^{N-1} x_n \exp(-jn\omega T_s)^2 = \frac{1}{N} \left| X_n(\omega) \right|^2.$$ (4)

In Equation 4, the estimate of the power spectral density as a function of the angular frequency $\omega$ is related directly to the observed data $x_t$. $X_n(\omega)$ is the
Fourier transform of the data \( x_t \), \( N \) is the number of values in the observed set, \( T_s \) is the sampling interval, and \( j = \sqrt{-1} \).

Since the data are discrete, \( x_i \) denotes samples taken from a continuous time function \( x(t) \), that is,

\[
x_i = x(nT_s) \quad n = 0, 1, 2, \ldots, N-1.
\]

Similarly, in the computations, discrete values of the angular frequency \( \omega \) are used

\[
x(\omega) = X(m\Omega_s) \quad m = 0, 1, 2, \ldots, N-1
\]

where \( \Omega_s = \frac{2\pi}{NT_s} \) is the frequency spacing of the data. Equation 4 means that the various frequency components of the signal contribute their power additively and independently to the total power of \( x(t) \).

Analyses were performed on a PDP 11/70 computer (Digital Equipment Corporation, Maynard, Massachusetts), which provided graphic and printed output. \(^{18}\) Indices obtained for each analysis and employed in this study were the autocorrelation and the maximum of the power spectrum. A plot of typical outputs in a normal subject and a patient with essential hypertension is shown in Figures 1–3. The autocorrelation \( (R_r) \) is commonly defined as:

\[
R_r = \frac{1}{N-r} \sum_{t=r}^{N-1} x_t x_{t+r} \quad (r = 0, 1, 2, \ldots, m) \quad (5)
\]

where \( r \) = lag number, \( m \) = maximum lag number, and \( N \) is the number of samples. The autocorrelation provides a quantitative measure of oscillatory behavior: the autocorrelograms for the two studies shown in Figure 1 are given in Figure 2.

As the index of the magnitude of oscillatory activity we have employed the normalized power, which is defined in Equation 3. To assess the frequency of the oscillations we have used the cycle length, which is the inverse of the frequency of the maximum amplitude defined in the Fourier transformation.

![Figure 1. Tracings of xenon transit through the kidney in a typical normal subject (left) and a patient with essential hypertension (right). The line of best fit was based on the method of maximum likelihood.](image)

![Figure 2. The autocorrelation function for the data presented in the two subjects in Figure 1. The excellent autocorrelation indicates the presence of distinct oscillations for both cases, with a similar period length. Data presented are tracings from the computer output.](image)
The normalized signal, on which the Fournier transformation was made, and the power spectrum analysis for the same two cases shown in Figure 1 and 2. Note the similarity in the data except for the striking difference in the maximum amplitude of the normalized signal and the power spectra. The dotted lines represent a three-point smoothing of the data.

Results

Despite the similarity in age and gender distribution and the systematic exclusion of patients with advanced hypertension associated with a reduction in renal excretory function, mean renal blood flow was significantly lower in the patients with essential hypertension (299 ± 8 ml/100 g/min) than in the normal subjects (335 ± 6 ml/100 g/min; t = 3.48; p < 0.001; Table 1). Normalized power, the index of oscillatory behavior of xenon transit through the kidney, was more than twice as large in the patients with essential hypertension as in the normal subjects (Table 1). There was no difference in the frequency or cycle length of the oscillation (Table 2). The frequency distribution of normalized power in all the normal subjects and patients with essential hypertension is shown in Figure 4.

Variation in arterial blood pressure also did not account for periodicity in xenon transit. In Figure 5, for example, mean arterial blood pressure is shown during the blood flow study in 10 patients with pronounced

### Table 1. Renal Hemodynamics in Essential Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Normal</th>
<th>Essential Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RBF (ml/100 g/min)</td>
<td>Normalized power</td>
</tr>
<tr>
<td>Total subjects</td>
<td>335 ± 6</td>
<td>1.70 ± 0.20</td>
</tr>
<tr>
<td>Sequential</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>319 ± 22</td>
<td>1.29 ± 0.22</td>
</tr>
<tr>
<td>2nd</td>
<td>310 ± 18</td>
<td>1.58 ± 0.33</td>
</tr>
<tr>
<td>Thigh cuff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>337 ± 31</td>
<td>1.27 ± 0.18</td>
</tr>
<tr>
<td>Cuff</td>
<td>305 ± 18††</td>
<td>1.71 ± 0.23</td>
</tr>
<tr>
<td>Emotional stress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>319 ± 14</td>
<td>2.76 ± 0.6</td>
</tr>
<tr>
<td>Stress</td>
<td>330 ± 16††</td>
<td>4.65 ± 3.61††</td>
</tr>
</tbody>
</table>

RBF = renal blood flow. Values are means ± SEM.

*P < 0.05; **P < 0.01; ***P < 0.001 for essential hypertension vs normal.

†P < 0.05; ††P < 0.01; †††P < 0.001 for control vs experimental run.
oscillations in xenon transit. Normalized power exceeded 7.0 in these patients. Perfusion pressure ranged from 91.5 ± 6.8 to 95.6 ± 8.4 mm Hg during the 3 minutes of xenon transit, and no evidence of phasic change was evident either in the individuals or in the group as a whole. Similarly, there was no evidence of a phasic alteration in heart rate.

No correlation could be found (Table 3) between the abnormality in normalized power and the patient's age, blood pressure, renal perfusion, sodium excretion, plasma renin activity (84 patients), or plasma catecholamines (42 patients).

In sequential studies in 12 normal subjects and 19 patients with essential hypertension, there was no significant difference between the first and second run in renal blood flow or the frequency of the oscillation in normalized power (Tables 1 and 2). Reproducibility was excellent.

When cuffs were inflated high on the thighs, to trap blood and thus provide a physiological stimulus to renal vasoconstriction, a different pattern of response appeared in the normal subjects compared to the patients with essential hypertension. The reduction in renal blood flow in the normal subjects was smaller than the reduction in the patients with essential hypertension (p < 0.01). In the normal subjects, the increase in normalized power (1.3 ± 0.2 vs 1.7 ± 0.3) did not achieve statistical significance. In the patients with essential hypertension, there was a significant increase in normalized power (1.97 ± 0.73 vs 4.97 ± 1.70; p < 0.025).

Responses to the emotional stress tests were complex. Renal blood flow did not fall in the normal subjects (319 ± 14 vs 330 ± 16 ml/100 g/min) but did fall in the patients with essential hypertension (368 ± 24 vs 291 ± 21 ml/100 g/min; p < 0.001). In the patients with essential hypertension, with the fall in renal blood flow the normalized power rose (2.98 ± 0.63 vs 20.10 ± 4.77; p < 0.005). An unanticipated increase in normalized power (2.76 ± 0.61 vs 14.65 ± 3.60; p < 0.005) also occurred in the normal subjects despite the unchanged renal blood flow.

### Table 2. Cycle Length

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Normal (sec)</th>
<th>Hypertensive (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>144</td>
<td>40.6 ± 1.4</td>
<td>44.4 ± 1.9</td>
</tr>
<tr>
<td>Sequential</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh cuff</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>15</td>
<td>35.6 ± 3.0</td>
<td>33.4 ± 4.1</td>
</tr>
<tr>
<td>2nd</td>
<td>15</td>
<td>46.8 ± 5.6</td>
<td>46.1 ± 4.2</td>
</tr>
</tbody>
</table>

Figure 4. Distribution of normalized power in normal subjects and in patients with essential hypertension. Note that the abscissa is a log scale.

Figure 5. Relationship of normalized signal and autocorrelation functions to mean blood pressure (BP) and heart rate in 10 patients with essential hypertension in whom normalized signal was large and the period was virtually identical. Note that the oscillation in xenon transit is not evident either in the perfusion pressure or in the heart rate.
TABLE 3. Correlation of Possibly Relevant Variables with Normalized Power

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>100</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>100</td>
<td>0.09</td>
<td>NS</td>
</tr>
<tr>
<td>BP (at study)</td>
<td>100</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>BP (on admission)</td>
<td>100</td>
<td>0.12</td>
<td>NS</td>
</tr>
<tr>
<td>BP (highest recorded)</td>
<td>100</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>100</td>
<td>0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>84</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>42</td>
<td>0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma epinephrine</td>
<td>42</td>
<td>0.07</td>
<td>NS</td>
</tr>
</tbody>
</table>

Discussion

Oscillation in the rate at which xenon traverses the kidney is difficult to interpret in any way except in terms of phasic changes in renal perfusion. Earlier studies in which serial determinations of renal perfusion were performed in normal humans are consistent with this finding. In normal subjects, serial determinations of blood flow showed an absolute difference that was larger than could be accounted for on the basis of analytic error. A similar phenomenon, but enhanced in degree, was also apparent in patients with essential hypertension, consistent with observations in this study. Moreover, a potentiated response to several vasodilators in patients with essential hypertension, evident both in measurement of renal blood flow and in the characteristics of the renal arteriogram, is also consistent with this view. Thus, this study provides additional evidence for a low-grade vasomotion that is more pronounced in patients with essential hypertension than in normal humans.

We examined two alternative possibilities that might account for the phasic transit of xenon, periodicity in perfusion pressure and periodic recirculation of xenon, but we ruled these out as determinants. In the absence of any other explanation for the phenomenon, we suggest that vasomotion, an intrarenal event, must be the cause.

Multiple studies have documented a potentiated vascular response to vasoconstrictor stimuli in animal models and in patients with hypertension. In general, the studies in humans have been confined to the vascular beds of the extremities. Our study clearly extends the evidence for enhanced reactivity to the renal vascular bed. In normal subjects, the trapping of a substantial volume of blood in the limbs with venous tourniquets led to the anticipated reduction in renal blood flow, but the reduction was considerably less than in patients with essential hypertension. The results are in accord with our earlier documentation of an enhanced response of the renal blood supply to an emotional stimulus.

Evidence in these studies suggests that the oscillation in renal perfusion is not a simple function of reduced renal blood flow or active renal vasoconstriction. The reflex response to trapping of blood in the limbs in the normal subjects was sufficient to reduce renal blood flow significantly, but was not associated with an increase in the rate or amplitude of the oscillations, whereas the stimulus induced a striking increase in normalized power in the patients with essential hypertension. It seems unlikely that the enhanced response in essential hypertension merely reflected the larger fall in renal blood flow, as there was an overlap in the response. In the normal subjects in whom the largest reduction in renal blood flow occurred — a reduction that was similar in magnitude to that in some patients with essential hypertension — the fall was not associated with an increase in normalized power, whereas it was in the patients with hypertension. Moreover, oscillatory activity in the transit of radioxenon through the normal human kidney rose during the emotional stimulus, despite the failure of renal perfusion to fall, which provides further evidence of a dissociation between the fall in renal blood flow and the oscillatory behavior.

The phasic response could reflect either periodic local release of the responsible mediator, perhaps catecholamines or renin, or periodicity in the response to the mediator. A wide variety of mediators of periodicity has been documented in biological systems. Examples include rhythmic fluctuations in the intracellular concentration of calcium, of cyclic AMP, or adenosine triphosphate (ATP).

The striking increase in oscillatory amplitude induced by two maneuvers likely to lead to reflex activation makes catecholamines an attractive possibility. A recent review of central nervous system oscillators responsible for sympathetic nerve discharge provides a possible explanation for our observations. Brain-stem and spinal networks that are responsible for sympathetic nerve discharge have an inherent capability for rhythm generation. Not only did our patients with essential hypertension differ from the normal subjects in baseline oscillatory activity, but the addition of stimuli likely to induce a reflex response enhanced their oscillatory activity substantially more and produced a larger reduction in renal blood flow. The data are consistent with an abnormality in the central nervous system control of the renal circulation, which is present in the basal state and which is enhanced during reflex activation.

Oscillations must reflect synchronization and require simultaneous contractile responses of many renal vessels. If the stimulus is exogenous as in the rhythmic release of norepinephrine, for example, the phasic vascular response is easily understood. If not, the data would suggest a pacemaker function. Because the frequency of the response was not altered under any of the circumstances studied, the data would support an enhanced vascular response to pacemaker activity. A possible contribution of pacemaker activity has been cited to account for phasic responses in other
vascular systems\textsuperscript{6} and to support the myogenic concept of the control of renal vascular tone.\textsuperscript{3,5}

What are the implications of these observations? First, they provide strong evidence for an important element of active vasoconstriction that involves the renal blood supply in patients with essential hypertension, and additional evidence that favors an enhanced renal vascular response to vasoconstrictor stimulation. Second, in an earlier study we noted that oscillatory renal perfusion was evident primarily in patients with processes such as hepatic cirrhosis and glomerular nephritis, which have as a common feature a tendency for the kidney to retain sodium.\textsuperscript{14} Whether in essential hypertension, too, there is an association between short-term periodicity in renal perfusion and a tendency for sodium retention remains to be evaluated. All of these observations and possibilities should be considered in the current investigations of the role of the kidney in sustaining hypertension, however the hypertension is initiated.\textsuperscript{34,35} The relevance of such observations to the pathogenesis of essential hypertension would then be obvious.

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References

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