Renal Vasomotion in Essential Hypertension: Influence of Vasodilators

Norman K. Hollenberg, Tamas Sandor, Eliezer Holtzman, Michael F. Meyerovitz, and Donald P. Harrington

To assess factors responsible for phasic behavior of renal blood flow in essential hypertension, we applied an analytic method based on the estimation of power spectral density to xenon transit through the kidney and examined the renal vasodilator response to a range of agents in 53 normal subjects and 53 patients with essential hypertension. The renal vasodilator response to the calcium channel blocking agent diltiazem, but not the response to alpha-adrenergic blockade (phentolamine) or angiotensin converting enzyme inhibition (teprotide or captopril), was associated with a significant reduction in the amplitude of renal vasomotion. Acetylcholine, a vasodilator that acts through the release of a vasorelaxant factor or factors from endothelium, induced an unanticipated increase in renal vasomotion. These observations further dissociate factors responsible for basal renal vascular tone and periodic changes in renal vascular tone and raise the possibility that abnormalities in the flux of calcium into renal arterioles contribute to increased renal vasomotion in essential hypertension. (Hypertension 1989;14:9-13)

A regular periodicity in blood flow, for which the term “vasomotion” has been coined, occurs as a feature in a number of vascular beds.1-5 We have described, in patients with essential hypertension, an increase in the amplitude of renal blood flow oscillations that exceeded substantially the amplitude identified in normotensive subjects.2 Several internal lines of evidence suggested that sympathetic nervous system activity contributed to renal vasomotion in essential hypertension.5 The vasoactive agents norepinephrine and angiotensin II increased the amplitude of blood flow oscillations in normal subjects when infused continuously in doses adequate to reduce renal blood flow suggesting that phasic release of a mediator was not necessary to induce a phasic response.6 In the present study, we attempted to identify possible mediators of increased vasomotion in essential hypertension by assessment of the action of agents that antagonize the renal vascular response to norepinephrine and to angiotensin II. We also examined the response to acetylcholine, a vasodilator that acts through an unrelated mechanism, and to diltiazem, a calcium channel blocking agent.

Subjects and Methods

We studied 53 patients who had essential hypertension and 53 normal subjects with use of techniques we have described in detail elsewhere.5-7 All subjects were admitted to a metabolic ward where a thorough evaluation ruled out significant cardiovascular, adrenal, or intrinsic renal disease in the normal subjects. The metabolic ward has a separate diet kitchen that made it possible, by maintaining each subject on a 10 meq sodium intake, to achieve external sodium balance in each subject included in the study. Daily 24-hour urine collections were employed to assess sodium excretion and sodium balance. Essential hypertension was established on the basis of a detailed evaluation to identify 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 to rule out a renovascular cause of hypertension; normal subjects also underwent renal arteriography 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 approximately 0.4 ml 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-in. cylindrical collimator oriented so as to avoid inclusion of the lung in the field. The peak counts in the first study always exceeded 2,000 counts/sec and exceeded background by a factor of at least 300. When a second study was performed, the count rate always exceeded 5,000 counts/sec and exceeded background by a factor of 200. A second matched scintillation detector was placed over the thigh to identify a contribution due to recirculation of xenon. Only minor recirculation occurred, and it was neither 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 for the continuous measurement of arterial blood pressure with a pressure transducer (model P23Dc, Gould Statham 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, the latter with a cardiotachometer (Electronics for Medicine).

Based on the maximum likelihood principle, a computer algorithm was developed to determine the line of best fit and statistical error. The counts in most subjects revealed significant sinusoidal variations, which were superimposed on the washout curve and the line of best fit. The properties of the superimposed variation were analyzed by estimation of their power spectral density, which described the frequency decomposition of the average power.

A convenient measure of the average power is the mean square value of individual deviations 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, and the line of best fit. To have a common unit of measure, we introduced a normalization procedure in the computation of average power; this index is termed the "normalized power". The signals were approximated by means of a suitably chosen periodic function. We employed Fourier analysis, where these are sine and cosine functions. By computation of the estimate of the power spectral density, the average signal power was decomposed into contributions from harmonics. Normalization of the data is equivalent to a scaling of the difference signal by the standard deviation, for counts that obey a Poisson distribution. As a second index, we employed the "power-filtered" signal. This index is identical to that provided by normalized power, but it is restricted to the largest harmonic identified by the Fourier transformation. Although secondary modes were occasionally identified, every curve was characterized by a dominant primary mode that had a cycle length of about 40 seconds.

Analyses were performed on a VAX computer (Digital Equipment Corporation, Maynard, Massachusetts), which provided graphic and printed output. Indexes obtained for each analysis and employed in this study were the autocorrelation and the maximum of the power spectrum.

We used the normalized power and power-filtered signal as the index of the magnitude of oscillatory activity. To assess the frequency of the oscillations, we used the cycle length, which is the inverse of the frequency of the maximum amplitude defined in the Fourier transformation.

The vasodilator agents employed included the $\alpha$-adrenergic blocking agent phentolamine, the converting enzyme inhibitors teprotide and captopril, the endothelium-dependent vasodilator acetyicholine, and the calcium channel blocking agent diltiazem. Phentolamine was infused into the renal artery in doses of 100–300 $\mu$g/min in six patients with essential hypertension and in eight normal subjects. Teprotide was administered intravenously as a rapid bolus over about 3 minutes, in a dose of 10–25 $\mu$g/kg in six patients and in eight normal subjects. Captopril was given orally in a dose of 10–25 mg in eight patients and 10 normal subjects. Acetylcholine was infused into the renal artery at a rate of 10–100 $\mu$g/min in eight patients and eight normal subjects. Diltiazem was infused directly into the renal artery in a dose of 30–300 $\mu$g/min in six patients and seven normal control subjects. In each case, the data used for analysis were selected because the dose that was employed increased renal blood flow by 20–35%. A similar convention was used in the selection of the normal subjects for each agent, except the studies with phentolamine, since phentolamine, even at the largest dose employed (1,000 $\mu$g/min), did not increase renal blood flow in the normal subjects.

Mean values are presented with the standard error of the mean as the index of dispersion. The paired $t$ test was employed for intragroup comparisons, and analysis of variance for comparison of responses to the vasodilator agents.

All protocols were approved by the Human Subjects Committee of the Brigham and Women's Hospital, and written, informed consent was obtained in each case.

Results

In the normotensive subjects, renal blood flow increased by the selected 20–35% in each group with the exception of the placebo-treated individuals and those treated with phentolamine, in whom renal blood flow was unchanged. Normalized power in the normotensive subjects was unchanged by phentolamine, teprotide, or captopril, in doses ade-
TABLE 1. Renal Hemodynamic Responses

<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>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12</td>
<td>319±22</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>310±18</td>
</tr>
<tr>
<td>Phentolamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8</td>
<td>357±32</td>
</tr>
<tr>
<td>Agent</td>
<td></td>
<td>350±41</td>
</tr>
<tr>
<td>Teprotide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8</td>
<td>321±16</td>
</tr>
<tr>
<td>Agent</td>
<td></td>
<td>350±41</td>
</tr>
<tr>
<td>Captopril</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10</td>
<td>344±22</td>
</tr>
<tr>
<td>Agent</td>
<td></td>
<td>420±36</td>
</tr>
<tr>
<td>Acetylcholine</td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8</td>
<td>367±33</td>
</tr>
<tr>
<td>Agent</td>
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<td>462±44</td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7</td>
<td>323±15</td>
</tr>
<tr>
<td>Agent</td>
<td></td>
<td>408±14</td>
</tr>
</tbody>
</table>

Values are mean±SEM. RBF, renal blood flow.

*p<0.0001 for comparison of differences in r between normal subjects and patients with essential hypertension.

RBF, to have achieved substantial blockade of either responses to norepinephrine, on the one hand, or angiotensin formation on the other (Table 1). Acetylcholine infusion in the normotensive subjects induced an unanticipated, significant increase in normalized power (p<0.001), despite an increase in renal blood flow that differed little from those induced by the converting enzyme inhibitors or the calcium channel blocker diltiazem.

Normalized power tended to fall in the patients with essential hypertension treated with the α-adrenergic blocking agent phentolamine and the converting enzyme inhibitor captopril, but none of the decrements achieved statistical significance and a similar fall occurred in the placebo group. In each group, at least two subjects showed an increase, rather than the anticipated decrease. Acetylcholine induced an increase in normalized power that occurred in every case in the essential hypertensive patients (p<0.01) as was the case for the normotensive subjects receiving acetylcholine.

Diltiazem sharply reduced normalized power in each of the hypertensive patients treated, and in individual cases, the reduction was evident by inspection of the xenon transit data (Figure 1).

Power-filtered signal showed changes in exact accord with those changes shown by normalized power. In the acetylcholine-treated normotensive subjects, normalized power rose from 0.48±0.02 to 1.28±0.07 (p<0.01). In the patients with essential hypertension treated with acetylcholine, power-filtered signal rose from 1.23±0.27 to 3.01±0.07 (p<0.01).

Neither blood pressure nor heart rate changed during infusion of the vasoactive agents in any subject, or for the group as a whole. Cycle length,
as in previous studies, ranged from 35 to 49 seconds and was unchanged in any of the subgroups during infusion of vasoactive agents or placebo infusions.

Discussion

As we have reviewed in detail in our earlier publications on this subject, it is difficult to interpret the oscillation in the rate at which xenon traverses the kidney in any way other than as a reflection of phasic changes in renal perfusion. Recirculation of xenon cannot account for the phenomenon, and variation in urine or lymph flow is too small to have made a contribution. As in earlier studies, blood pressure was measured continuously during the assessment of xenon transit and did not change. The periodic behavior of xenon transit must reflect a phasic change in blood flow due to active changes in the vascular smooth muscle.

Our working premise in the present study was that norepinephrine was the responsible mediator; hence, we anticipated finding that phenolamine-induced increases in renal blood flow, which we had reported in some patients with essential hypertension, would be associated with a reduction in the amplitude of the oscillation. Our reasons for suspecting that norepinephrine was responsible include 1) the large number of studies that have documented an influence of norepinephrine on vasomotion in a number of vascular smooth muscle preparations in vitro and in vivo, 2) the influence on renal vasomotion of maneuvers such as application of thigh cuffs that are likely to elicit a reflex response, and 3) the striking influence of norepinephrine in inducing an increase in renal vascular vasomotion in our earlier studies. Certainly, the dose of phenolamine employed in this study was more than adequate to achieve substantial α-adrenergic blockade.

As a second premise, we had anticipated that angiotensin II might be the responsible mediator. Converting enzyme inhibitors induce a striking increase in renal blood flow in a substantial number of patients with essential hypertension, which exceeds the normal response. There has been substantially less interest in the contribution of angiotensin II than norepinephrine to active vasomotion, but our earlier study did document an increase in response to angiotensin II in normal subjects, albeit substantially less than that induced by norepinephrine. Converting enzyme inhibition was also ineffective in reversing the active vasomotion despite the use of doses that produce a clear reduction in the rate of angiotensin II formation.

An unstated, but evident premise underlying this study was the possibility that the factors underlying an increase in the basal level of renal vasomotion in this study would be identical to the factors responsible for an increase in renal vasomotion induced by various maneuvers. The results of this study make that possibility much less likely.

Interest has been expressed in the possibility that endothelium-dependent relaxation is abnormal in at least some hypertension models. Acetylcholine-induced vasodilatation, the paradigm of endothelium-dependent responses, was examined in this study as a control for the other vasodilators, and the response was not anticipated. Acetylcholine did not reduce the amplitude of the oscillations; indeed, the amplitude of the oscillations increased. It is tempting to speculate on the possible relations between the unanticipated acetylcholine-induced increase in vasomotion and the increase in vasomotion that occurs in essential hypertension, but no basis for speculation on the mechanism of the unanticipated response to acetylcholine is available.

There has also been interest in the role of calcium as a mediator of phasic contractile responses in various systems. Diltiazem, the calcium channel blocking agent, induced a substantial and consistent reduction in the amplitude of the renal vasomotion in the patients with essential hypertension. No pharmacological agent has absolute specificity, and there is no internal evidence in this study to indicate that diltiazem acted to reduce renal vasomotion through its influence on calcium flux, but that interpretation is certainly consistent with a substantial body of investigation on the role of calcium in active vasomotion.

Further, this study also serves to dissociate active renal vasomotion from renal blood flow per se, providing support for the interpretation of earlier studies. In the case of the comparison of angiotensin and norepinephrine, the latter induced a substantially larger influence on the amplitude of vasomotion despite the fact that angiotensin induced a somewhat larger reduction in renal blood flow. In this study, a series of vasodilator agents produced a renal blood flow increase in the same range as that induced by diltiazem, but without an influence on the amplitude of vasomotion. Indeed, acetylcholine-induced vasodilatation was associated with a paradoxical, unanticipated increase in renal vasomotion.

There has been substantial interest in the possibility that abnormalities in calcium flux or intracellular calcium contribute to the abnormalities in vascular tone that occur in essential hypertension. The results of this study confirm that possibility and extend it to the renal blood supply. Given the potential importance of the renal blood supply in the initiation and maintenance of hypertension, the findings could have implications for pathogenesis.

References


**KEY WORDS** • acetylcholine • phentolamine • diltiazem • endothelium-dependent relaxation • captopril • teprotide • norepinephrine • angiotensin II • calcium channel blocker
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