Baroreceptor Activity in Normotensive and Hypertensive Uremic Patients

By J. M. Lazarus, M.D., C. L. Hampers, M.D., E. G. Lowrie, M.D., and J. P. Merrill, M.D.

SUMMARY

Baroreceptor activity and postural blood volume changes were evaluated in four normotensive and nine hypertensive uremic patients before and after bilateral nephrectomy. Baroreceptor activity, reflected by the slope of linear regression of R-R interval with drug-induced systolic blood pressure elevation, was significantly lower in hypertensive than in normotensive patients. Six of nine patients had normal blood pressure following bilateral nephrectomy; however, the mean slopes of all nine patients, irrespective of postnephrectomy blood pressure, approached that of normotensive uremic patients. The slopes of both normotensive and hypertensive patients, before and after bilateral nephrectomy, were significantly less than normal controls. Similar results were found in lowering blood pressure with amyl nitrite.

Depressed baroreceptor activity is suggested to be secondary to neuropathy of the autonomic nervous system, chronic hypertension, heart disease, and anemia. It is speculated that this reduced baroreceptor sensitivity may accentuate the postural symptoms primarily induced by volume reduction on hemodialysis. There is no evidence in this study that depressed baroreceptor activity, as opposed to a reset baroreceptor, is a cause of hypertension in patients with chronic renal failure.

Additional Indexing Words:
Renoprival hypertension Uremia Baroreceptor Hypertension A.N.S. neuropathy
Bilateral nephrectomy Postural hypotension

HYPERTENSION can be controlled in the majority of patients with terminal renal failure by reduction of extracellular volume with hemodialysis. In the small percentage of patients not responsive to ultrafiltration, bilateral nephrectomy has proven successful. Recent evidence indicates that those hypertensive hemodialysis patients with elevated renin levels respond more predictably to bilateral nephrectomy, thereby incriminating the renin-angiotensin system as a cause of elevated blood pressure. The etiology of hypertension in the normovolemic anephric patient and normovolemic prenephrectomy patient with normal renin levels is unknown. Resetting of the baroreceptor mechanism has been suggested as a cause for elevated arterial pressure in patients with chronic renal hypertension and renoprival hypertension, and perhaps is the etiology of this nonrenin, nonvolume dependent hypertension. Recent information by Pickering, Gribbin, and Oliver suggests that baroreflex sensitivity changes very little at different arterial pressures in a group of chronic uremic patients, indicating resetting of the reflex.

We have observed in some hypertensive dialysis patients abnormal vascular responses—widely fluctuating blood pressures during hemodialysis and postural hypotension with supine hypertension while on no antihypertensive medication. In a pilot study of 140 hemodialysis patients, blood pressures 48 hours after dialysis, taken in the recumbent position, and immediately after standing, revealed an increase in postural changes of mean and diastolic pressures of hypertensive patients (table 1). This pilot study suggested hypertensive patients on hemodialysis, both before and after bilateral nephrectomy, have abnormal postural blood pressure changes while normotensive uremic patients

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differ only slightly from controls. This was felt to be due primarily to contraction of extracellular volume with rigorous ultrafiltration in hypertensive patients; however, the role of an abnormal baroreceptor, already suggested to be of etiologic importance in the hypertension, was questioned as a factor in the postural changes. This paper reports the effect of uremia and hypertension on the baroreceptor mechanism in hemodialyzed patients.

**Methods**

Thirteen hemodialysis patients, consecutively selected only on the basis that they were preparing to undergo bilateral nephrectomy, were studied to evaluate more critically the response of baroreceptor mechanism to elevation and reduction in arterial pressure induced by change in posture and with pharmacologic agents. Patients were divided into the appropriate blood pressure group based on history and demonstration of hypertension before initiation of and during adequate hemodialysis. Hypertension, defined as systolic pressure greater than 150 mm Hg and diastolic pressure greater than 90 mm Hg, had been present at least 1 year. Studies on each patient were performed at a time when extracellular volume was estimated to be normal and at least 48 hours following the last hemodialysis. Methyldopa, the only antihypertensive medication used in three patients, was discontinued at least 1 week prior to study. The indication for nephrectomy in the normotensive patients was preparation for transplantation. Informed consent was obtained from all patients.

Patients were placed in the recumbent position for 30 min and arterial pressure was measured from the arterial side of a Scribner A-V shunt via a Statham P-23 pressure transducer. Respiations were measured with a pneumograph and the R-R interval was measured from lead I of an electrocardiogram. These parameters were recorded simultaneously using a Gilson polygraph. The venous side of the A-V shunt was kept patent with a slow dextrose and water drip (less than 20 cc during the study).

To evaluate the effect of posture on plasma volume, samples for hematocrit, serum sodium, serum osmolality, total serum protein, and albumin-tagged $^{131}$I plasma volume were taken with patients in the supine position. Blood pressure, respiration, and pulse rate was simultaneously recorded, and the patient placed in the standing position. After 15 min in the upright position, the above studies were repeated.

Patients were returned to the recumbent position and when blood pressure, pulse rate, and respirations had stabilized, received an angiotensin bolus through the venous limb of the A-V shunt. In most instances, an increase in systolic blood pressure of 30–50 mm Hg was adequate to create a change in the pulse rate; however, in two cases up to 100 mm Hg were necessary. The dose required ranged from 0.25 to 1.0 μg of angiotensin. Simultaneous electrocardiogram, respirations, and systolic pressure were measured with each drug administration. This procedure was repeated twice after return of all parameters to baseline values. Three
similar recordings were made following single inhalation of an amyl nitrite ampule which caused a drop in systolic pressure of 30-50 mm Hg. Patients were carefully monitored during the transient manipulations of blood pressure and the procedure terminated if any symptoms developed.

Baroreceptor activity was interpreted from the pulse response (R-R interval) to changes in systolic pressure as described by Smyth, Sleight, and Pickering and Bristow, Honour, Pickering, Sleight, and Smyth. R-R intervals were measured during expiration to eliminate the effect of sinus arrhythmia and systolic pressures were measured two beats prior to each R-R interval. Linear regression of the R-R interval systolic pressure was performed by method of least-squares utilizing all points in the three determinations. Smyth et al. suggested that the slope of a line relating R-R intervals to systolic pressure elevated with pressor agents reflects the sensitivity of baroreceptor mechanism and the position of the regression along the blood pressure axis represents "resetting." Each patient underwent the above study before and 3-6 months following bilateral nephrectomy.

Five normal volunteers underwent percutaneous brachial artery catheterization for measurement of arterial pressure while simultaneous respiratory and R-R interval measurements were obtained. The average age was 25, while that of the patients was 34 years. These subjects were normotensive and had no history or symptoms of postural hypotension. Compared to uremic patients, they required much smaller doses of angiotensin and amyl nitrate to develop blood pressure and R-R interval changes.

Significant differences were screened for each test by variance analysis. If the resultant F indicated differences between groups (normal controls; prenephrectomy normotensive uremic patients; postnephrectomy normotensive uremic patients; prenephrectomy hypertensive uremic patients, and postnephrectomy hypertensive uremic patients) \( P < 0.05 \), the differences were identified by Duncan's Multiple Range Test. Student's paired t test was employed where appropriate.

**Results**

Four of the 13 patients studied in detail had never been hypertensive nor treated for hypertension. Their pressures on multiple determinations with sphygmomanometers averaged 143/58, while the average blood pressure in the five normal controls was 124/74. The average intraarterial systolic pressures of the four normotensive uremic patients, however, was approximately 60 mm greater than the five normal controls. This was felt to be due partially to real differences in pressure, but to a great extent due to differences in the measurement of blood pressure through the percutaneous needle as compared to the indwelling arterial shunt. The remaining nine uremic patients had significant histories of hypertension prior to and after the initiation of hemodialysis. With bilateral nephrectomy, six of the nine became normotensive and remained so throughout the remainder of their hemodialysis treatment.

Table 2 outlines the effect of upright posture on hematocrit, serum osmolality, serum sodium, serum protein, and albumin-tagged \(^{131}I\) plasma volume in both hypertensive and normotensive uremic patients before and after nephrectomy. Twenty min after assuming the upright position all patients had consistent and significant \( P < 0.02 \) increases in hematocrit and total serum protein by paired analysis. Although albumin-tagged \(^{131}I\) plasma volume determinations varied with an SEM of 0.5 liters, a decrease was seen with standing in normotensive patients and postnephrectomy hypertensive patients \( P < 0.01 \). Serum sodium and osmolalities did not change. Mean changes of the five test parameters from lying to standing did not differ significantly between test groups by analysis of variance. Changes in hematocrit, total protein, and \(^{131}I\) plasma volume together indicate that there is a slight reduction in plasma volume with assumption of upright position, but the magnitude of this change is not significantly different in hypertensive and normotensive uremic patients. The differences in response to posture between normotensive and hypertensive uremic patients is therefore on the basis of differences in intravascular volume induced by hemodialysis and not due to differences in volume caused by the level of blood pressure. Changes in plasma volume with upright posture were not affected by removal of diseased kidneys.

In these 13 patients, the change in systolic and diastolic arterial pressures on assuming the upright position was noted. In this small group average orthostatic hypotension in normotensive uremic patients (systolic = \(-17.9 \pm 6.2\); diastolic = \(-5.4 \pm 3.0\) mm Hg) was not significantly different from hypertensive uremic patients (systolic = \(-29.8 \pm 9.7\); diastolic = \(-9.9 \pm 4.8\) mm Hg); however, both were significantly greater than normals (systolic = \(-4.98 \pm 1.24\); diastolic = \(+3.08 \pm 1.82\) mm Hg). Linear regressions of the R-R interval vs change in blood pressure with standing were without significant correlation. On the other hand, pharmacologically induced changes in blood pressure usually resulted in pulse changes which related to the pressure change with a high degree of significance.

Patients tolerated elevations of approximately 30-100 mm Hg in systolic pressure and 30-50 mm of pressure drop without difficulty. Individual and
mean slopes in each of the groups are listed in Table 3. Angiotensin test slopes illustrated in Figure 1 indicate that prior to nephrectomy the mean angiotensin slope of the hypertensive patients ($b = -1.263$) is significantly less ($P < 0.01$) than the normotensive group ($b = +2.106$). After bilateral nephrectomy the average reduction in systolic blood pressure in the nine hypertensive patients was 36 mm Hg. This reflects a "resetting" of the slope down the systolic scale. The mean slopes after nephrectomy in hypertensive ($b = -0.031$) and normotensive ($b = +2.106$) patients are not significantly different from their respective prenephrectomy values by paired analysis. The six hypertensive patients who became normotensive with surgery have a mean postnephrectomy slope of $b = -0.312$, and the three postnephrectomy persistently hypertensive patients a mean slope of $b = +0.529$. The latter figure is not significantly different from the mean slope of the prenephrectomy or either postnephrectomy normotensive group. The mean slopes of hypertensive and normotensive uremic patients before and after nephrectomy are all significantly less ($P < 0.01$) than that observed in normal subjects. Figure 2 illustrates similar slopes developed by lowering blood pressure with inhalation of amyl nitrite. This maneuver reveals no significant difference between the mean slopes of the four uremic groups; however, they are all significantly lower ($P < 0.01$) than the mean slope of normal individuals given amyl nitrite.

![Figure 1](image)

**Figure 1**

*Comparison of the mean slopes of linear regressions developed by blood pressure elevation with angiotensin in normal subjects, normotensive uremic patients before and after bilateral nephrectomy, and hypertensive uremic patients before and after bilateral nephrectomy.*
**Table 3**

**Linear Regression Slopes before and after Bilateral Nephrectomy**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Angiotensin slope</th>
<th>Amyl nitrite slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre nephrectomy</td>
<td>Post nephrectomy</td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uremics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.984</td>
<td>2.617</td>
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<tr>
<td>2</td>
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<tr>
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<tr>
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<tr>
<td>Mean ± SEM</td>
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<td>1.483 ± 0.418</td>
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<tr>
<td>Hypertensive</td>
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<td>uremics</td>
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<tr>
<td>Mean ± SEM</td>
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<td>-0.031 ± 0.437</td>
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<tr>
<td>Normal subjects</td>
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</tr>
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<td>5</td>
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<tr>
<td>Mean ± SEM</td>
<td>9.083 ± 1.254</td>
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</tr>
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</table>

**Discussion**

The 13 patients studied did not experience symptomatic postural hypotension; however, all had measurable decreases in blood pressure with standing which was significantly greater than in normals. In five normal subjects given angiotensin the slope of the line relating R-R intervals to systolic pressure was found to be \( b = +9.083 \), which approaches that of normal subjects reported by Bristow et al.\(^{20}\) and Eckberg, Brabinsky, and Braunwald.\(^{23}\) The effect on the baroreceptor function of lowering blood pressures has not been previously examined. In normal controls we found the slope of the linear regression with pressure lowered by amyl nitrite to be \( b = +9.129 \), which is essentially the same as the slope with blood pressure elevation. The mean slope of the 13 uremic patients is significantly lower than that derived in normal individuals given amyl nitrite. Within the uremic group there are no significant differences between the mean slopes of the four subgroups.

The mean slope with angiotensin was significantly less in hypertensive patients than that in normotensive patients prior to bilateral nephrectomy. In fact, negative slopes were found in some hypertensive uremic patients. We have no explanation for this finding but consider it possibly due to the combined effects of hypertension and uremia. Following bilateral nephrectomy and lowering of blood pressure in six of nine patients, the mean slope of the hypertensive group became insignificantly different from the normotensive group.

![Comparison of the mean slopes of linear regression developed by blood pressure lowering with amyl nitrite in normal subjects, normotensive uremic patients before and after bilateral nephrectomy, and hypertensive uremic patients before and after bilateral nephrectomy.](image)
suggesting the reduced blood pressure had allowed some improvement in baroreceptor function. However, the mean slope of the three patients who remained hypertensive after bilateral nephrectomy also improved and was not significantly different from the mean slope of the six hypertensive patients who became normotensive or the four who were initially normotensive. One might expect these three patients to continue to exhibit slopes lower than the other groups if altered baroreceptor were important in the etiology. It is possible, although unlikely, that nephrectomy, independent of its effect on hypertension, caused the apparent improvement in slope of these three patients. The discrepancy in these three patients might be explained by the small sample size and large standard error of the mean.

Linear regressions, developed with both elevation and lowering of blood pressure in hypertensive and normotensive uremic patients (before and after nephrectomy) had mean slopes all significantly lower than the mean slope of normal individuals. The normal controls had intraarterial blood pressures lower than the normotensive uremic patients which was possibly due to a difference in the technic of pressure measurement. Differences in the mean slopes of normal controls and normotensive uremics was felt, therefore, not to be on the basis of apparent differences in blood pressure. Based on the work by Gribbin et al.24 examining the effect of age on baroreflex sensitivity, it was felt the 9 year average age difference in controls and study patients was not a significant contributing factor.

Eckberg et al.21 studying patients with heart disease found a linear regression relating R-R interval to systolic pressure with a mean slope of 4.4 and concluded that the baroreceptor abnormality reflected a profound abnormality in the parasympathetic cardiovascular regulation in heart disease. Heart disease-induced changes in baroreceptor function could be important in the baroreceptor abnormality in these uremic patients. Three to 6 months after nephrectomy, two of the nine hypertensive patients continued to have obvious clinical evidence of heart disease and both had persistent hypertension. The four normotensive patients had no history or evidence by examination, chest X-ray, or electrocardiogram of hypertensive cardiovascular disease, arteriosclerotic heart disease, or uremic myocardopathy during this study. Hematocrits were low in these 13 patients and were further decreased with bilateral nephrectomy. The chronic anemia was compensated for by increase in extracellular volume and there was no resting tachycardia. The effect of chronic stable anemia on baroreceptor function is unknown but certainly might play a role.

Another possible explanation for the abnormality of baroreceptor response in these patients is that of uremic neuropathy of the autonomic nervous system. Hennessy and Siemsen25 found impaired eccrine sweat gland function in uremic patients who also had somatic neuropathy. Abnormal autonomic nervous system function has been demonstrated in uremic patients responding to the Valsalva maneuver and pilocarpine26 and atropine.27 We suggest that the blunted baroreceptor function demonstrated here may also be evidence of neuropathy of the autonomic nervous system.

In conclusion, uremic patients have a blunted baroreceptor response to pharmacologically induced blood pressure changes. Hypertensive patients have blunted and reset baroreceptor mechanisms which, following bilateral nephrectomy, tend to correct approaching that seen in normotensive patients. One cannot incriminate an altered baroreceptor as the cause of hypertension since the baroreceptor activity in the persistently hypertensive patients was not different from that in normotensive patients. It is apparent that a "reset" linear regression as measured here simply reflects the blood pressure level at which the study was initiated. We concur with Pickering, Gribbin, and Oliver18 that there is a persistently altered sensitivity at different blood pressure measurements; however, we feel this does not necessarily represent cause and effect. The evidence, although not supportive, does not exclude the possibility that a "reset" as opposed to blunted baroreceptor sensitivity plays some role in the hypertension of these patients.

In neither the hypertensive nor the normotensive uremic patient does removal of the kidneys and correction of hypertension correct the slope of linear regression to that seen in normal individuals. It is theorized that these uremic patients have blunted baroreceptor responses due to a combination of factors—neuropathy of the autonomic nervous system, heart disease, chronic hypertension, and chronic anemia. Postural hypotension seen in hypertensive uremic patients on hemodialysis is undoubtedly due primarily to contracted extracellular volume induced by ultrafiltration but is possibly accentuated by a blunted baroreceptor sensitivity.
BARORECEPTOR ACTIVITY IN UREMICS

References


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