Essential Hypertension: Abnormal Renal Vascular and Endocrine Responses to a Mild Psychological Stimulus

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SUMMARY We have assessed the influence of a mild emotional stimulus on arterial blood pressure, heart rate, renal blood flow, plasma renin activity (PRA), and plasma aldosterone concentration in 24 normal subjects, eight of whom had a parent with hypertension, and in 15 patients with essential hypertension. A nonverbal IQ test, Raven's Progressive Matrices, was employed as the stimulus. In 11 of the 15 hypertensives, arterial blood pressure rose transiently by 7 mm Hg or more, but in only three of 16 normal subjects ($\chi^2 = 7.23, p < 0.01$). Transient moderate increases in heart rate were also more common in the hypertensives ($p < 0.01$). Renal blood flow rose in 11 of 16 normal subjects and fell in each of the 15 patients with essential hypertension ($\chi^2 = 15.1; p < 0.005$). As opposed to the transient changes in arterial pressure and heart rate, the fall in renal perfusion was sustained. The PRA fell in 10 of the 16 normal subjects with a negative family history and rose in 14 of 15 patients with essential hypertension ($p < 0.005$). Changes in plasma angiotensin II concentration and in plasma aldosterone were in accord with the changes in PRA, but plasma cortisol did not change. Both the renal vascular response and the change in PRA were intermediate in normal subjects in whom family history was positive for hypertension. For the entire group of 39 subjects there was statistically significant agreement between the direction of the renal vascular response and the directional change in PRA: renal blood flow rose when PRA fell and fell when PRA rose ($p < 0.005$). We conclude that there is an abnormality in the control of both the renal circulation and of renin release in patients with essential hypertension in response to psychological provocation, and that a similar process is present in some normotensive subjects whose parents have hypertension. (Hypertension 3: 11-17, 1981)

Key Words • emotions • renal vasculature • plasma renin activity • plasma aldosterone • familial hypertension

ESSENTIAL hypertension remains a disease of unknown pathogenesis. As for many processes in which the cause is obscure and which may be exacerbated by stressful circumstances, investigators have repeatedly claimed that psychological, especially emotional, factors play a pathogenetic role — perhaps the key role. As reviewed recently, this conclusion has lacked credibility to many for a number of reasons: the conclusions were often based on subjective and uncontrolled observations and the stimuli employed were often gross and poorly reproducible. Moreover, the index employed was often only the pressor response, and because the blood pressure response to vasoconstrictor agents is also enhanced in essential hypertension, it has been reasonable to suspect that the enhanced pressor response to emotional stimuli was nonspecific.

Because psychological stimuli are difficult to apply in a controlled and even semiquantitative fashion, we attempted to deal with these limitations in this study by employing Raven's Progressive Matrices, a nonverbal IQ test first employed by Nestel for this purpose. The result was a stimulus too mild to produce a sustained increase in blood pressure. Our focus, however, was on the underlying renal vascular and related endocrine responses rather than the direct pressor effect of the stimulus.

Recent advances have again directed our attention to the kidney as a pathogenetic factor in sustaining hypertension whatever its cause. Two earlier studies have documented an accentuated renal vascular response to a major, disturbing stimulus in patients with hypertension. We have extended the documentation to both an enhanced renal vascular response and renin release provoked by even a mild stress similar in degree to those that form the fabric of our everyday lives. An unanticipated finding was that...
normotensive subjects whose parents had hypertension frequently demonstrated a renal response that resembled that of patients with essential hypertension, but smaller in magnitude and reduced in duration. Viewed in the context of evidence that suggests an important inherited factor in the pathogenesis, this observation is consistent with a hypothesis in which the renal response in essential hypertension was not a consequence of long-standing hypertension, but rather could be present at its origin.

Methods

Subjects

The 24 normal subjects were all potential kidney donors ranging in age from 22 to 66 years (38.9 ± 3.9 years) and requiring selective renal arteriography as part of their assessment. All were carefully screened for cardiovascular, renal, or adrenal disease. In eight, a history of hypertension in one or both parents was obtained. The 15 patients with essential hypertension ranged in age from 22 to 65 years (40.1 ± 4.0 years). None had received antihypertensive medication for at least 4 weeks prior to study.

All were admitted to a metabolic ward where a thorough history and physical examination were obtained and detailed laboratory investigation was performed as described. The detailed assessment we use to diagnose essential hypertension by exclusion has been described. In brief, a thorough history and physical examination were followed by a laboratory investigation that included in the examination a fresh urinary sediment, quantitative urine cultures, 24-hour urine collections for the determination of excretion of vanillylmandelic acid, metanephrines, 17 hydroxy and 17 keto steroids, protein, and the clearance of creatinine. Serum electrolyte, urea nitrogen, creatinine, glucose, uric acid, calcium determinations, aldosterone, renin, and cortisol as well as a complete blood count were obtained routinely. Routine examination also included a chest film, electrocardiogram, bolus high dosage intravenous pyelogram, and renal arteriogram in all patients included in this study. The clinical indications for arteriography were those generally cited, with an unusual age of onset being the most common indication in this group and previously undiagnosed essential hypertension in the potential donor being next. Obtaining details of the family history was facilitated by distributing a ROCOM questionnaire (Roche Laboratories) prior to admission, with instructions that multiple family members be consulted concerning family history of disease, which included hypertension.

Sodium intake was restricted to 10 mEq/day and potassium intake fixed at 100 mEq/day in all of the patients with essential hypertension. An identical protocol was used in 14 of the normal subjects, including the eight with a hypertensive parent, but because of a wide range of plasma renin activity (PRA) in the patients with essential hypertension, in five of the potential kidney donors a 200 mEq sodium intake was utilized to reduce PRA. In an additional five donors, potassium intake was restricted to 40 mEq/day along with restricted sodium intake, to provoke a higher control PRA. All subjects were on the diet for at least 5 days, and were in balance at the time of the study.

Techniques

Urography, selective renal arteriography, and renal blood flow assessed by the xenon washout technique were performed according to methods we have described. Arterial catheterization and aortography were completed 60 minutes or more prior to initiating the physiological studies. Arterial blood pressure and the electrocardiogram heart rate were monitored continuously with a Statham P23 Dc Transducer connected to the catheter and recorded on an Electronics in Medicine polygraph. Blood pressures reported represent the mean of a 1-minute sample taken at each blood flow determination, assessed by an individual who was not aware of either the patients' diagnosis or the protocol sequence. PRA, plasma angiotensin II, aldosterone, and cortisol concentrations were measured by radioimmunoassay. Plasma and urine creatinine and sodium and potassium concentrations were measured by the autoanalyzer method.

Protocols

Written informed consent was routinely obtained prior to this study. The subjects were told that we know of an important interaction between the mind and body, and that the object of the study was to assess body function while the mind was otherwise occupied. To that end we described a "game" designed to occupy them, which would be played during the study. The game would consist of a series of projected slides that posed a question and demanded a spoken answer. As long as they were answering questions, they were told, we knew that their mind was occupied with the game.

The slides were back-projected via a prism onto a 10 X 10 in. screen with a commercial system (Singer Caramate). The slides shown during the first 6 minutes consisted of optical illusions that the subjects were asked to identify. During the next 20 minutes the subjects were shown a series of slides derived from Raven's Progressive Matrices, a nonverbal IQ test designed to free the assessment of IQ from education and social factors. The matrices consist of a series of spatial puzzles of increasing difficulty; the subjects were to choose from among eight solutions provided and were urged to answer as quickly as possible. Renal blood flow was assessed at intervals through the procedure (see fig. 1 for timing). Blood pressure and heart rate were monitored continuously. Arterial blood samples were drawn for determinations of plasma angiotensin II, aldosterone, and cortisol concentrations and PRA prior to and at the end of the study.

Means have been presented with the standard error of the mean (SEM) as the index of dispersion. Statistical significance was assessed with the Student t
The normal subjects with a family history negative for essential hypertension, normal subjects with a positive family history, and patients with essential hypertension differed by analysis of variance in only one respect in the control period to the study (table 1). Mean arterial pressure, not surprisingly, was significantly higher in the patients with hypertension (98 ± 3.8) mm Hg; \( p < 0.01 \), than in either the family history negative (81 ± 2.7 mm Hg) or in family history positive (88 ± 4.6 mm Hg) normotensive subjects. The basal renal blood flow, PRA, angiotensin II concentration, aldosterone, and cortisol did not differ in any of the groups (table 1).

During performance of the game a clear difference in the pattern of the response between the normal subjects with a negative family history, the normal subjects with a family history positive for hypertension, and the patients with essential hypertension became apparent (figs. 1 and 2). Mean renal blood flow fell strikingly, by an average of 80 ± 14 ml/100 g/min, in the patients with essential hypertension \( p < 0.01 \) and the fall was well-sustained (fig. 1). In the normal subjects with a negative family history, a small but statistically significant increase in renal blood flow occurred \( p < 0.01 \). In the normotensive subjects in whom a family history of hypertension was present, renal blood flow fell, but tended to return toward control values as the game evolved (fig. 1).

When average values for mean arterial blood pressure and heart rate at the predetermined intervals were used, no change in mean arterial pressure was evident in any group (fig. 1). For the largest increase in blood pressure, however, averaged over 1 minute at these predetermined times, a clear difference was apparent; essential hypertensives showed a significantly greater tendency to a pressor response (fig. 2). Blood pressure rose by 7 mm Hg or more in 11 of 15 hypertensives, but in only three of 16 normal subjects \( (x^2 = 7.23, p < 0.01) \). A similar pattern was evident for the change in heart rate \( p < 0.01 \).

Control PRA in the family history negative normal subjects (4.6 ± 0.69 ng/AI/ml/hr) differed neither from that in the normal subjects with a positive family history (3.6 ± 0.27 ng/AI/ml/hr) nor in the patients with essential hypertension (5.9 ± 1.1 ng/AI/ml/hr). As the game was played, however, a striking difference in the pattern appeared (figs. 2 and 3). The

![Figure 1. The response of renal blood flow (RBF), arterial blood pressure (BP), and heart rate (PR) to the mild emotional stress provoked by performing a nonverbal IQ test. Raven’s Progressive Matrices.](image)

The protocols were approved by the Peter Bent Brigham Hospital and Harvard University Human Experimentation Committees, and written informed consent was obtained routinely.

### Results

The normal subjects with a family history negative for essential hypertension, normal subjects with a positive family history, and patients with essential hypertension differed by analysis of variance in only one respect in the control period to the study (table 1). Mean arterial pressure, not surprisingly, was significantly higher in the patients with hypertension (98 ± 3.8) mm Hg; \( p < 0.01 \), than in either the family history negative (81 ± 2.7 mm Hg) or in family history positive (88 ± 4.6 mm Hg) normotensive subjects. The basal renal blood flow, PRA, angiotensin II concentration, aldosterone, and cortisol did not differ in any of the groups (table 1).

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### Table 1. Characteristics of the Subjects Prior to Study

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects</th>
<th>Family history negative</th>
<th>Family history positive</th>
<th>Subjects with essential hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP (mm Hg)</td>
<td>81 ± 2.7</td>
<td>88 ± 4.6</td>
<td>98 ± 3.8*</td>
<td></td>
</tr>
<tr>
<td>RBF (ml/100 g/min)</td>
<td>332 ± 19</td>
<td>305 ± 14</td>
<td>319 ± 25</td>
<td></td>
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<tr>
<td>PRA (ng AI/ml/hr)</td>
<td>4.6 ± 0.69</td>
<td>3.6 ± 0.27</td>
<td>5.9 ± 1.11</td>
<td></td>
</tr>
<tr>
<td>AI (pg/ml)</td>
<td>32.3 ± 4.9</td>
<td>41.0 ± 6.4</td>
<td>35.8 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>25.4 ± 8.8</td>
<td>14.3 ± 2.1</td>
<td>18.6 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>Cortisol (μg/dl)</td>
<td>12.73 ± 1.6</td>
<td>22.2 ± 6.0</td>
<td>13.4 ± 2.5</td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>16</td>
<td>8</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

*\( p < 0.01 \).

BP = blood pressure; RBF = renal blood flow; PRA = plasma renin activity; AI = angiotensin II.
FIGURE 2 Changes in renal blood flow, arterial blood pressure (BP), and plasma renin activity (PRA) provoked by Raven's Progressive Matrices. In this case the arterial BP response was the largest documented during the procedure, and the data for mean renal blood flow and PRA represent changes from the control period to the end of the procedure.

PRA was unchanged or fell in 10 of the 16 normal subjects with a negative family history and rose in 14 of the 15 patients with essential hypertension (MWUT; p < 0.005). A correlation was found (fig. 3) between the control PRA (X) and PRA at the end of the game (Y) in the family history negative normotensive subjects (Y = 0.82X + 0.30; r = 0.91; F = 65.4; p < 0.01) and in the patients with essential hypertension (Y = 1.44X + 0.88; r = 0.96; F = 183; p < 0.001). The slope from these equations differed significantly, rising in the essential hypertensives (1.44 ± 0.10 SD) and falling in the normal subjects (0.82 ± 0.01 SD; t = 16.3; p < 0.02).

For the entire group of 39 patients, there was agreement between the direction of the renal vascular response and the directional change in PRA: among the subjects in whom renal blood flow fell, PRA rose in 88%. Conversely, PRA fell in 72% of those in whom renal blood flow rose (χ² = 7.90; p < 0.005).

The changes in plasma angiotensin II concentration were in accord with the results of PRA. Plasma angiotensin II fell in 10 of the 12 normal, family history negative subjects in whom the determination was available, which differed significantly from the rise that occurred in 13 of 15 patients with essential hypertension (+ 7.9 ± 2.8 pg/ml; p < 0.02).

Plasma aldosterone also fell significantly during the game in the family history negative normal subjects, to 15.1 ± 4.05 ng/dl (p < 0.01). A tendency for plasma aldosterone to rise in the patients with essential hypertension (to 21.1 ± 7.7 ng/dl) did not achieve statistical significance, but was significantly different from the pattern of the response in the normal subjects (p < 0.01). As for PRA, the control plasma aldosterone concentration was a determinant of the response (fig. 3). In contrast, no significant changes in plasma cortisol occurred in any group.

The normotensive subjects who had a parent with hypertension showed intermediate responses (fig. 2). Renal blood flow rose in only 3 of 8, vs 11 of 16 with a negative family history (p < 0.01). The PRA rose in 6 of 8, but in only 5 of 16 with a negative family history (p < 0.05). The difference in the pressor pattern did not achieve statistical significance.

Discussion
Various stimuli have been used in attempts to provoke an emotional response in man. For some, such as serial subtraction or the Stroop Color Test, it must be clear to the participants that the aim of the maneuver is to provoke or unsettle them. Our experience was that serial subtraction was too sensitive to the mood and personality of the investigator and the subject to serve as a reproducible stimulus. Our subjects were instructed that we were playing a game the purpose of which was to occupy their attention while we made certain physiological measurements; at no time were the terms stress or test employed. Nonetheless, patients with essential hypertension appeared to perceive the maneuver as stressful.
Because we interpreted their comments in an open rather than coded fashion, we have not subjected the data to formal analysis. A prospective, controlled study designed to assess the subjects' perception of the maneuver would be worthwhile, and is planned. One element in our results might indicate that the stress provoked by recognition of an IQ test was not central to the response: the optical illusions, which we in-
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FIGURE 3. Influence of control plasma renin activity and plasma aldosterone concentration on these indices at the end of the procedure. The slopes relating the control and final values were significantly steeper in patients with essential hypertension for both plasma renin activity (p < 0.01) (left) and plasma aldosterone concentration (p < 0.02) (right). Only the normal subjects without a family history of hypertension have been included.

Another methodologic problem may have contributed to the confusion. An important element of selection is built into the referral process, as is most clearly seen in the early literature on hypertension; patients selected for referral to a psychiatrist are not a random sample. Even among patients with hypertension, the forces that determine whether a patient will be referred to a medical center for a detailed clinical evaluation may well include their personality. In this study, six of the 15 hypertensives came to evaluation not because of their hypertension, which had not been diagnosed, but rather as potential kidney donors. The response in this subset differed in no way from the group as a whole: moreover, the similar response in normotensive subjects with a positive family history also suggests that we did not study a selected subset of hypertensives.

Earlier studies have demonstrated a potentiated renal vascular response to emotional stress in patients with hypertension, an observation confirmed and extended by this study. This study has documented, in addition, that a stress too small to induce a sustained blood pressure increase will provoke a striking and well-sustained reduction in renal blood flow in patients with essential hypertension. It may be important to recognize that the setting in which this study was performed, following arteriography in a cardiovascular catheterization laboratory, may have contributed to the results. The studies were performed at least 1 hour after the acute discomfort of arterial catheterization and aortography had waned and attempts were made to provide a neutral setting free of fear and discomfort: although overt emotional reactions were not evident, the situation is clearly potentially stressful. Indeed, it is reasonable to ascribe the increase in renal blood flow and fall in PRA and aldosterone concen-
tation to relief from the tension created by the setting. As an alternative, an increase in renal perfusion could be part of the normal adaptive response to a mild stress, as occurs for cardiac output.11

An increase in PRA has been documented in baboons during avoidance operant conditioning,19 in rats during exposure to a novel environment or the presence of a hungry cat,20 and in response to intermittent electrical shock21 and with aggressive behavior in mice.22 The animals were normotensive prior to the stimulus, and even large increases in PRA occurred in response to intermittent electrical shock and with aggressive behavior in mice. The animals were normotensive prior to the stimulus, and even large increases in PRA occurred. In our study the stimulus was too small to induce a PRA increase in the normal subjects or an increase in plasma cortisol in any group. Indeed, PRA fell significantly, again presumably because participating in the game focused the normal subjects’ attention away from the stressful situation. In the essential hypertensives, on the other hand, an increase in PRA occurred that was related both to the PRA prior to performing in the study and to the change in renal blood flow. Parallel directional changes in plasma angiotensin II concentration and in plasma aldosterone concentration provide further evidence for differential activation of this system and not the pituitary-adrenal axis in patients with essential hypertension.

Perhaps the most provocative observation made was the unexpected finding that some of the normotensive offspring of hypertensive parents showed a renal response that resembled that of hypertensives, although smaller in magnitude and less well sustained. A number of abnormalities have been documented in individuals in whom the family history is positive for hypertension. Such individuals show a potentiated vascular response to pharmacologic stimuli.23 It is possible that the potentiated vascular response in individuals in whom the family history is positive in the two earlier studies and this one reflects the phenomenon suggested by Folkow.27 Episodes of the sort documented in these studies may lead to thickening of the arteriolar wall which amplifies the vascular response to vasoconstrictors but which is too modest to result in sustained hypertension at this stage. With time, the vascular hypertrophy may become sufficiently pronounced so that the sustained increase in vascular resistance and hypertension are the consequence. Certainly, however, such an explanation cannot easily account for a potentiated increase in plasma catecholamines28 or in PRA, as in this study: nor could it account for abnormalities in erythrocyte electrolyte flux,29 in renal perfusion,29 or plasma volume30 in normotensive individuals whose parents have hypertension. The difficulty in separating cause and consequence once hypertension is established makes examination of their normotensive children especially attractive for dissecting pathogenesis.

The intense renal vasoconstriction raises at least three interesting questions. First, what mediators could have been responsible for the response? Second, is there any precedent for vasoconstriction involving the renal vasculature preferentially? Third, could the renal response play a pathogenetic role in the development of hypertension? Only partial answers are available for each. Nestel7 who employed the same stimulus, documented an increase in urinary catecholamine excretion that paralleled the pressor response: norepinephrine, via local neural release, could certainly have been responsible for the renal response, although the stimulus as we employed it was not pressor. As an alternative, local angiotensin formation as a consequence of the enhanced renin release could have been responsible for the renal vasoconstriction. Both possibilities are amenable to direct assessment with specific antagonists.

Whether the renal response was mediated directly by the action of norepinephrine on the renal vascular alpha receptors, or indirectly by angiotensin formation, it seems likely that the link between the emotional or psychic stimulus and the renal response was neural. The past two decades have seen the accumulation of evidence that suggests that discrete, focal responses to activation of different central neuron pools are common, and that diffuse firing occurs only when near maximal activation of the system is required.31-34 Indeed, the blood supply of the kidney, in particular, is subject to separate, independent central nervous system control.35-38 In view of the intense renal vasoconstriction without a systematic change in arterial blood pressure, an offsetting reduction in cardiac output or vasodilatation in other vascular beds must have occurred. Again, a substantial precedent for this exists: for example, dilatation in the vasculature of skeletal muscle is well documented during an emotional response.11 A reduction in cardiac output to account for the unchanged arterial blood pressure is less likely.39 Reasonable but unproved speculation would place the response in the category mediated by the “defense reaction.”50 Certainly emotional factors can activate this area and, as recently reviewed,41 important elements in that response include transient, mild pressor changes, a sharp reduction in renal blood flow, and striking renin release — as occurred in the patients with hypertension and some of the normotensive children of hypertensives studied. In their basal state, however, the characteristics of hypertensives are thought to be more characteristic of their coping style than of the emergency defense reaction.47

Investigators who have approached the problem of the pathogenesis of hypertension from widely differing viewpoints have found it difficult to achieve a synthesis without invoking a renal component.48-50 The abnormal responses documented in this study could play pathogenetic roles in one or more of several ways. Renal vasoconstriction, especially in concert with enhanced aldosterone release, could modify the state of sodium balance. Angiotensin formation could lead not only to a pressor response directly, especially in the presence of a somewhat expanded total body sodium, but has also been demonstrated to enhance the vascular response to sympathetic nervous system activation.50 The fact that the response occurred to a stimulus so mild, and that a qualitatively similar
response occurred in normotensive subjects whose parents had hypertension, provides an easy link between these observations and pathogenesis.

How can we weave these observations into our current understanding of the pathogenesis of hypertension in this syndrome? Psychological factors are best seen as one of a host of factors that interact with a predisposition, which at least in part is genetically predetermined. The fact that PRA and aldosterone concentration rose most strikingly in those who already carried the highest levels, for example, suggests that a biological amplification system was at work, enhancing responses rather than initiating them. To the extent that a reduced ability to cope with a stressful situation occurs in patients with essential hypertension, their response expressed in cardiovascular, renal, and endocrine indices is enhanced. The nature of the predisposition is likely to vary from person to person, or perhaps from family to family. The ease of application of the test and the excellent indices provided by measurement of PRA and aldosterone make prospective studies in the children of individuals with essential hypertension attractive. Will those who show this pattern of response go on to hypertension?

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