Cardiotoxic Effects of Hypercatecholemia in Renal Insufficiency

By W. RAAB, E. LEPESCHKIN, Y. K. STARChE5KA, AND W. GIGEE

Renal insufficiency is regularly accompanied by an increase of the total catecholamines of the blood. Adrenolytic drugs, which inactivate circulating catecholamines, temporarily improve the abnormal S-T segments and T waves in patients with renal insufficiency but not in hypertensive patients without renal complications. It is suggested that in renal insufficiency, the retained circulating catecholamines damage cardiac metabolism and function. In agreement with previous observations, the behavior of the "left ventricular strain pattern" was relatively independent of the blood pressure level.

ABNORMALLY high concentrations of catecholamines in the blood of patients with advanced renal insufficiency were described by one of us1 in 1944 and were subsequently confirmed by ourselves2 and other workers.3, 4 Emlet and associates5 reported an increased concentration of epinephrine in the blood in a case of uremia, and Manger and associates,4 who measured epinephrine and norepinephrine by means of fluorometry, found elevated blood levels of these substances in uremic patients, apparently in combination with other similar compounds.* Our colorimetric values, obtained with a modification of Shaw’s method,6 represent "total" catecholamines and include catechol compounds with still undefined pharmacodynamic properties beside epinephrine and norepinephrine.

The origin of the excess catecholamines in the blood of uremic patients needs further exploration, but it is probable that they accumulate in the circulation because of inadequate elimination by the damaged kidneys. Holtz6 found the urinary excretion of "urosympathin" to be diminished in cases of severe renal pathology and our own observations7 also suggested a deficiency of catecholamine excretion in the uremic state.

"False positive" tests for pheochromocytoma with phentolamine (Regitine) or piperoxan (Benzdioxone) have been recorded relatively frequently in cases of uremia.3, 7-10 A significant vasodepressor effect of these drugs in small diagnostic doses indicates the presence of abnormal amounts of catecholamines in the circulating blood. The comparatively common vasodepressor action of the "adrenolytic" drugs in uremic individuals seems to constitute a functional corollary to the hypercatecholemia mentioned above. An increase of the catecholamine concentration in the blood is also consistent with certain hemodynamic changes that develop in hypertensive patients when renal insufficiency supervenes,11 and with the toxic effects exerted on frog and other animal hearts by crude serum, serum dialyzates, and protein-free serum extracts from uremic patients.1, 12

Exposure of the hearts of patients with renal insufficiency to an excess of catecholamines is suggested by the usual electrocardiographic alterations, chiefly in the T waves and S-T segments. Similar changes are elicited by injection of epinephrine13-15 and also by experimental bilateral nephrectomy.16 The incidence of electrocardiographic abnormalities was

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Part of this work was done during the tenure by Dr. Lepeschkin of an Established Investigatorship of the American Heart Association.

* An increased concentration of epinephrine and norepinephrine in the blood of 5 uremic patients was also recently reported by A. Goldfien, S. Zileli and deW. Goodman (Trans. Endocrine Society, Abstracted, J. Clin. Endocrinol. 16: 940, 1956).
higher in hypertensive patients in whom renal biopsies revealed severe structural lesions than in patients with a minor degree of involvement of the kidneys.\textsuperscript{17}

The intact mammalian heart muscle is distinguished from the skeletal muscle by the avidity with which it absorbs catecholamines from the circulating blood.\textsuperscript{18} Accordingly, abnormally high catecholamine concentrations have been observed in the heart muscle of both nephrectomized animals\textsuperscript{19} and of patients who had died in uremia.\textsuperscript{1, 5} In the latter, this increase seems to concern mainly catechol compounds other than epinephrine and norepinephrine.\textsuperscript{18, 20} It is not regularly observed, however,\textsuperscript{21} possibly because the capacity of the metabolically and structurally damaged myocardium to absorb catecholamines from the blood may be diminished before death.

In order to obtain further evidence of the participation of excess circulating catecholamines in the origin of cardiovascular abnormalities, occurring in uremia, we investigated the effect of the adrenolytic drugs Regitine and phenoxybenzamine (Dibenzyline) on both the blood pressure level and the electrocardiogram of hypertensive patients with and without signs of renal excretory insufficiency and hypercatecholemia.

**Material and Methods**

Two groups of patients were studied: 19 cases of essential hypertension (blood pressures of 160–280/100–160 mm Hg) without major renal complications were designated the "nonuremic" group, and 19 cases of hypertension with signs of renal excretory insufficiency were designated the "uremic" group. Indications of uremia were the following: a high blood urea (42–198 mg per cent) or nonprotein nitrogen (73–250 mg per cent), low excretion of phenolsulfonphthalein (51–8 per cent in 2 hours), low specific gravity of the urine (1.017–1.013), elevated serum potassium (4.9–7.7 mEq./1.), retinal lesions, and a high blood level of the colorimetrically determined total catecholamines (270–800 color units/ml). An additional number of previously reported\textsuperscript{1, 2, 5, 9} observations of catecholamines in normotensive and hypertensive individuals with and without renal insufficiency were added to these 2 groups.

Albuminuria was present in 14 of the 19 nonuremic cases and in all 19 uremic cases here reported. One of the nonuremic and 6 of the uremic patients were in congestive cardiac failure. None of the patients was digitalized or received barbiturates at the time of the tests.

After intramuscular injection of 10 mg. of Regitine* or oral administration of 80–100 mg. of Dibenzyline,\textsuperscript{1} both blood pressure and electrocardiogram were recorded until they returned toward their original state (about 1 hour for Regitine and several hours for Dibenzyline). In 1 case, 100 mg. of Regitine was also given by mouth. The values of total catecholamines in blood and heart muscle were determined with a modification of the colorimetric method of Shaw.\textsuperscript{5}

**Results**

**Total Blood Catecholamines.** In comparison with a series of 36 cases of essential hypertension without uremia, the values of the catecholamines in the blood in a series of 53 "uremic" cases were abnormally elevated (table 1). With 3 exceptions, all readings, obtained from the blood of "uremic" patients, were higher than the maximum seen in "nonuremic" hypertension.

**Blood Pressure.** The responses to Regitine of systolic and diastolic blood pressures varied between nil and marked depression in both patient groups, the average being nearly identical (table 2). The time intervals between injection and maximal response were also about the same in both groups. In 1 instance of malignant hypertension with renal insuffi-

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Type of cases & Number of cases & \multicolumn{2}{c|}{color units*/mL.} & \multicolumn{2}{c|}{color units*/gm.} \\
\hline & & Range & Average & Range & Average \\
\hline Normal & 51 & 90–222 & 156 & 72 & 275–1641 & 1290 \\
Hypertension without renal complications & 36 & 60–257 & 154 & 30 & 923–2443 & 1683 \\
Hypertension with renal insufficiency & 53 & 146–800 & 404 & 23 & 1652–2197 & 1749 \\
\hline
\end{tabular}
\caption{Total Catecholamines in Human Blood and Heart Muscle}
\end{table}

* Supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

\textsuperscript{1} Supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.
TABLE 2.—Reaction of Blood Pressure to Adrenolytic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Nonuremic hypertensive cases</th>
<th>Uremic hypertensive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of cases</td>
<td>Maximal fall of blood pressure (mm. Hg)</td>
</tr>
<tr>
<td>Regitine</td>
<td>10 mg. i.m.</td>
<td>18</td>
<td>±0 to −97*/±0 to −30 (mean −20/−10)</td>
</tr>
<tr>
<td>Dibenzyline</td>
<td>80–100 mg. p.o.</td>
<td>3</td>
<td>−15 to −36/−4 to −25 (mean −28/−16)</td>
</tr>
</tbody>
</table>

* This occurred in a patient with an exceptionally labile blood pressure that varied spontaneously between 148 and 245 mm. systolic and 90 and 114 mm. diastolic.

TABLE 3.—Changes in Electrocardiograms and Heart Rates After Adrenolytic Drugs in Nonuremic and Uremic Groups of Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>Changes in electrocardiogram</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Regitine</td>
<td>(10 mg. i.m.)</td>
<td>Improved</td>
<td>Ambiguous</td>
</tr>
<tr>
<td></td>
<td>Nonuremic hypertensive cases</td>
<td>0</td>
<td>3 cases (all LVS)</td>
</tr>
<tr>
<td></td>
<td>Uremic hypertensive cases</td>
<td>8 cases (all LVS)</td>
<td>3 cases (all LVS)</td>
</tr>
<tr>
<td>Dibenzyline</td>
<td>(80–100 mg. p.o.)</td>
<td>Nonuremic hypertensive cases</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Uremic hypertensive cases</td>
<td>3 cases (all LVS)</td>
<td>0</td>
</tr>
</tbody>
</table>

Average changes in heart rate

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>Changes in heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regitine</td>
<td>(10 mg. i.m.)</td>
<td>+18</td>
</tr>
<tr>
<td></td>
<td>Nonuremic hypertensive cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uremic hypertensive cases</td>
<td></td>
</tr>
<tr>
<td>Dibenzyline</td>
<td>(80–100 mg. p.o.)</td>
<td>+2</td>
</tr>
</tbody>
</table>

LVS = Left ventricular strain pattern; BBB = Bundle-branch block.

iciency, 100 mg. of Regitine, taken by mouth, caused a marked fall of the blood pressure (fig. 1).

Dibenzyline was given to 4 nonuremic patients and to 3 "uremic" patients, again with similar blood pressure reactions in both groups (table 2).

Electrocardiogram. The electrocardiographic ventricular patterns of the "nonuremic" hypertensive patients remained unchanged after Regitine in 6 cases, and showed an increased S-T and T depression in 10 cases that was coincident with an acceleration of the heart rate (table 3). In no instance was there a clear-cut improvement or return to normal of S-T or T. Slight, ambiguous alterations were seen in 3 cases. The reactions to Dibenzyline (4 cases) resembled those to Regitine.

By contrast, there was only 1 instance of Regitine-induced aggravation of the S-T depression in the "uremic" group. In this patient, the increase of the heart rate was greater than in any of the other cases of this group. Regitine caused a transient positive shift of S-T or T
in 8 out of 19 uremic cases (figs. 1 to 4). In 7 instances, the electrocardiogram remained unchanged, while in 3 the improvement was ambiguous. As a rule, the heart rate was significantly increased during the action of Regitine (figs. 1 to 4).

In all 3 uremic patients who received Dibenzyline, the electrocardiogram was improved for several hours.

The partial or complete return to normal of the ventricular complexes coincided sometimes with a fall of the blood pressure, but outlasted it (fig. 1) or occurred without it in some instances (fig. 3). In 1 case of labile hypertension with renal insufficiency, the deeply inverted T wave remained unaltered during a spontaneous reduction of the blood pressure to normal, whereas Regitine improved it, despite persistence of a high blood pressure level (fig. 4).

**Discussion**

Using 5 mg. of Regitine intramuscularly, the diagnostic dose for pheochromocytoma, Emlet and associates in did not observe any "false positive" blood pressure responses in cases of uncomplicated hypertension, whereas the blood pressure fell significantly in 5 of 11 uremic patients. With our higher dosage, we observed blood pressure reductions in both groups.

The aggravation of S-T and T-wave changes in more than one half of the nonuremic cases can probably be explained by the cardiac acceleration that was usually evoked by these
HYPERCATECHELOMIA IN RENAL INSUFFICIENCY

Fig. 2. Elevation of T wave during Regitine action coincident with lowered blood pressure in a case of Kimmelstiel-Wilson syndrome with renal insufficiency and hypercatecholemia.

The relative independence of the electrocardiographic “left ventricular strain pattern” from the blood pressure level (figs. 3 and 4) is in agreement with previous observations.15, 25-27 Thereby the view is confirmed that the electrocardiographic manifestations of “hypertensive” heart disease, especially the S-T and T changes, are largely due to a catecholamine-induced chemical effect and not merely to the mechanical “strain,” imposed by a high blood pressure. Epinephrine is known to decrease the ventricular gradient and to lower or invert the T wave in animals as well as in normal human subjects.13, 14

Despite the apparent ability of Regitine and Dibenzyline to protect the heart muscle of uremic patients temporarily from the presumably hypoxia-producing effects of extra circulating catecholamines, the prolonged administration of Regitine (up to 500 mg./day by mouth) and Dibenzyline (up to 250 mg./day by mouth) was therapeutically wholly

drugs. They augment rather than reduce the stores of intrinsic norepinephrine in the myocardium.28

By contrast, with 1 exception, the electrocardiographic abnormalities were not increased in the uremic patients by the adrenolytic drugs. Rather, a partial or complete return of the electrocardiogram to normal occurred during their action, despite cardiac acceleration. This improvement suggests that excess circulating catecholamines were temporarily prevented from contributing to the sum total of injurious metabolic effects of catecholamine action on the heart muscle. The nature of these metabolic effects of the catecholamines on the myocardium has recently been reviewed by one of us.22 In some animal experiments,23 Dibenamine and other adrenolytic drugs diminished or suppressed the S-T and T-wave changes that were induced by infusion of catecholamines. An analogous effect occurred with combinations of norepinephrine and Regitine.24
ineffective, probably because of a rapidly developing tolerance.

Morphologic observations in uremic patients and in animals with severe renal insufficiency suggest that the excessive total catecholamines, including epinephrine and norepinephrine, not only threaten the functional efficiency and survival of the heart but also contribute to degenerative structural alterations of the myocardium15 and of the vascular system.28, 29

**SUMMARY**

Renal insufficiency has been found to be regularly accompanied by hypercatecholemia. Therefore the effect of adrenolytic drugs (Regitine, Dibenzyline) on the blood pressure and electrocardiogram (mostly “left ventricular strain pattern”) was compared in 19 cases of essential hypertension with unimpaired kidney function, and in 19 hypertensive patients with renal excretory insufficiency.

The responses of the blood pressure to the drugs varied within a wide range in both groups.

In 56 per cent of the nonrenal cases, the S-T and T changes of the electrocardiogram were aggravated by the adrenolytic drugs, coincident with cardiac acceleration; in no instance were they improved. In contrast, they were temporarily improved or returned to normal despite cardiac acceleration in 42 per cent of the patients with renal insufficiency; in only 1 instance of this latter group were they aggravated.

Since the adrenolytic drugs are known to inactivate catecholamines that circulate in the blood but not those that are stored within the myocardium, the contrasting electrocardio-
HYPERCATECHELOMIA IN RENAL INSUFFICIENCY

E.C. 63 YRS. B.U.N.: 47 mg% - BLOOD CATECHOLAMINES: 270 col. un./cc
1/30/55
REGITINE 10 mg i.m.
MINUTES 10 20 30 40 60 90
BLOOD PRESSURE
120 110 100 90 80 70 60
HEART RATE
180 160 140 120 100 80

2/2/55 SPONTANEOUS
Elevation of T wave during Regitine action without a significant fall of the blood pressure in a case of nephrosclerosis with renal insufficiency and hypercatecholemia. A spontaneous drop of the blood pressure failed to produce a similar return toward normal of the electrocardiogram.

Graphic reactions in the 2 groups suggest an important contributory role of the circulating extra catecholamines in the origin of the electrocardiographic abnormalities in cases of renal insufficiency with “hypertensive” heart disease.

The relative independence of changes in the “left ventricular strain pattern” from the blood pressure level indicates that they are largely biochemical and not merely mechanical in origin.

SUMMARIO IN INTERLINGUA

Le effecto de drogas adrenolytic (Regitina, Dibenzylin) super le pression sanguinee e le electrocardiogramma (generalmente a “configuration de effortio sinistro-ventricular”) esesva comparate in 19 casos de hypertension essential con function renal intacte e in 19 casos de hypertension con insufficientia excretori renal. Le studio esseva motivate per le previe constatation que insufficientia renal es regularmente accompaniate de hypercatecholemia.

Esseva trovate in ambe gruppos que le responsas de pression sanguinee al administrazione del drogas esseva multo variabile.

In 56 pro cento del casos non-renal, il habeva un aggravation del alteraciones S-T e T del electrocardiogramma como effecto del drogas adrenolytic. Iste effecto coincideva con acceleration cardiaic. Nulle caso de melioration del alterationes mentionate esesva notate. In contrasto con isto, le alterationes esesva temporarimente meliorate o reducete al norma, in respecto de acceleration cardiaic, in 42 pro cento del patientes con insufficientia renal. Un sol caso in iste secunde gruppo reageva per alterationes aggravate.

Viste le cognoscite facto que le drogas
adrenolytic inactive catecholaminas que circula in le sanguine sed non le catecholaminas que es immagasinate in le myocardio, le contrasto del reactiones electrocardiographiae in le 2 gruppis permette le conclusione que le excesso de catecholaminas circulante ha un importante function contributori in le genese del anormalitates in case of insufficientia renal con “hypertensive” morbo cardiac.

Le relative independentia del alterationes del “configuration de effortio sinistro-ventricular” ab le nivello del pression sanguine indica que ille alterationes es in grande mesura in natura biochimic e non simplemente mechanic.

REFERENCES


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