Diazoxide-induced stimulation of renin release in renal vein renin sampling

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Summary

1. The acute effect of diazoxide (150–300 mg, intravenously) on renal venous renin has been evaluated in forty-four patients with suspected renal hypertension.

2. In twenty-seven studies which showed no lateralization, diazoxide raised the mean peripheral renin to 175% of control ($P < 0.05$) but the renal vein renin ratio showed an insignificant change (1.15 to 1.21).

3. In seventeen studies which showed lateralization the increase in peripheral renin was similar, but mean renal vein renin ratio increased from 1.90 to 3.52 ($P < 0.005$), and the mean ratio of contralateral renal vein to peripheral renin showed no change (1.05 to 1.07), indicating persistence of contralateral suppression.

4. Diazoxide accentuates the distinction between lateralizing and non-lateralizing renal vein renin studies.

Key words: hypoplastic kidney, renal ischaemia, renin secretion, renovascular hypertension.

Introduction

Renal vein renin sampling can define a unilateral renal abnormality causally related to hypertension by demonstrating predominant renin secretion from the affected kidney, with suppression of contralateral secretion as shown by comparable renin values in caudal inferior vena cava and contralateral renal vein (Stockigt, Collins, Noakes, Schambelan & Biglieri, 1972; Vaughan, Bühler, Laragh, Sealey, Baer & Bard, 1973). However, basal recumbent samples may give inconclusive results if renin secretion is low at the time of sampling (Vaughan et al., 1973).

Several stimulatory manoeuvres, including sodium restriction (Strong, Hunt, Sheps, Tucker & Bernatz, 1971), upright posture (Michelakis & Simmons, 1969) and infusion of sodium nitroprusside (Kaneko, Ikeda, Takeda & Ueda, 1967) have been found to accentuate lateralization. In the present study the renin-stimulating vasodilator drug diazoxide, has been evaluated as an adjunct to renal vein renin sampling in the basal recumbent sodium-replete state.

Methods

Sampling from renal veins and caudal inferior vena cava was performed in forty-four patients with suspected renal hypertension after overnight recumbency, on sodium intake ad libitum with a single catheter. Sampling was repeated 8–12 min after a bolus intravenous injection of 150–300 mg of diazoxide. The drug was not used in patients with a recent history of cerebrovascular insufficiency or suspected carotid artery stenosis. Diazoxide (300 mg) was used in the initial ten studies but the dose was reduced to 150 mg after an episode of prolonged hypotension. Renin findings were similar with 150 and 300 mg doses and results have been combined for analysis.

Anti-hypertensive therapy had been discontinued at least 3 days before study, except in one patient with renal artery stenosis studied while taking propranolol (40 mg daily) and two patients with essential hypertension studied while taking α-methyldopa (750 mg daily).

Plasma renin activity was measured by radio-immunoassay of angiotensin I as described pre-
viously (Stockigt et al., 1972), giving a normal range for peripheral renin of 1-4-5-6 nmol h$^{-1}$ l$^{-1}$ in sodium-replete recumbent normal subjects.

Results were evaluated by peripheral renin value, ratio of higher to lower renal vein renin value ($R/R_c$) and ratio of contralateral to peripheral renin value ($R_c/P$). Renal vein renin ratios greater than 1-5 were classified as showing lateralization. Paired data were evaluated by Student's $t$-test.

**Results**

Mean blood pressure fell from 129 (SEM 3, $n = 44$) to 107 (3) mmHg within the first 10 min after diazoxide. Blood pressure fall showed no correlation with renal pathology or renin status.

Of the forty-four studies, twenty-seven showed no lateralization, with a renal vein renin ratio less than 1-4 in both basal and post-diazoxide samples. In this group diazoxide raised the mean peripheral renin from 6.1 (1.5, $n = 27$) nmol h$^{-1}$ l$^{-1}$ to 10.6 (2.9) nmol h$^{-1}$ l$^{-1}$ ($P < 0.05$), but the renal vein ratio showed no significant change (1.15 to 1.21, $P > 0.5$).

In seventeen of the forty-four studies the renal vein renin ratio showed lateralization of secretion ($R/R_c > 1.5$). In thirteen cases lateralization was found in both basal and post-diazoxide samples, but in four cases asymmetry was seen only after diazoxide. In these seventeen studies the mean renal vein renin ratio ($R/R_c$) increased from 1-90 to 3-52 ($P < 0.005$) and the mean ratio of contralateral to peripheral renin showed no change after diazoxide (1.05 before, 1.07 after) (Fig. 1). In sixteen of these studies diazoxide raised the mean peripheral renin from 7.8 (1.6, $n = 16$) nmol h$^{-1}$ l$^{-1}$ to 12.8 (2.2) nmol h$^{-1}$ l$^{-1}$ ($P < 0.005$) and renin increased from 148 to 220 nmol h$^{-1}$ l$^{-1}$ in one other patient with renal artery obstruction.

Of these seventeen lateralizing studies, sixteen corresponded to a unilateral radiological abnormality as follows: renal artery stenosis (eight), unilateral hypoplastic kidney (three), unilateral hydronephrosis (two) and one case each of renal tuberculosis, renal cyst and segmental infarction. In one 13-years-old child consistent lateralization has been found without radiological abnormality. The eight patients so far treated operatively have shown a hypotensive response after follow up ranging from 2 to 30 months.

One of the four cases with lateralization only after diazoxide has so far been treated operatively. A 43-years-old woman with a 12 years' history of hypertension up to 240/130 mmHg has a blood pressure of 14/95 mmHg without treatment, 16 months after removal of a 7 cm hypoplastic right kidney weighing 30 g. Basal samples showed renin values of 1-3, 1-4 and 1-6 nmol h$^{-1}$ l$^{-1}$ in right and left renal veins and caudal vena cava, rising to values of 18-6, 11-0 and 9-7 nmol h$^{-1}$ l$^{-1}$ respectively after diazoxide.

**Discussion**

Diazoxide has been shown to stimulate renin secretion by a mechanism independent of change in plasma volume (Baer, Goodwin & Laragh, 1969) and its effect is at least partly mediated by adrenergic stimuli (Winer, Chokshi, Yoon & Freedman, 1969). The present findings indicate that diazoxide stimulates symmetrical renin secretion in hypertensive patients without a unilateral renal abnormality, while increasing the asymmetry of secretion in those with a significant unilateral renal lesion (Fig. 1). Similar changes can be induced by upright
tilting (Michelakis & Simmons, 1969) or sodium depletion (Strong et al., 1971), and these stimuli have been advocated to enhance the value of differential renin sampling. However, prior sodium depletion precludes sampling in both the basal and stimulated state during the same procedure, and tilting produces a short-lived spike of renin secretion (Michelakis, Woods, Liddle & Klatte, 1969), which necessitates simultaneous sampling with two catheters (Pawsey, Vandongen & Gordon, 1971).

Intravenous diazoxide produces a more sustained rise in peripheral renin, similar to that after sodium depletion and ambulation, with a maximum peripheral renin value between 1 and 3 h after injection (Küchel, Fishman, Liddle & Michelakis, 1967), and allows sampling in both the basal and stimulated state within a 30 min period. Serial renal vein and vena cava samples taken between 5 and 25 min after injection of diazoxide show qualitatively similar findings (J. R. Stockigt, E. J. Higgs & N. Sacharias, unpublished results), suggesting that valid post-stimulation samples can be taken with a single catheter.

In patients with a significant unilateral lesion there is persistence of contralateral suppression of renin secretion after this acute stimulus, as demonstrated by comparable values for renin in contralateral renal vein and caudal inferior vena cava (ratio Re/P near unity). The extent of suppression of contralateral renin secretion after an acute stimulus may be an indirect, but simple, way of assessing the state of the contralateral renal vasculature—a factor of great importance in determining the response to surgery (Fiorani, Faraglia, Benedetti-Valentini, Pistleolese, Semprebene, Spartera, Citone, Di Salvo & Cinotti, 1971).

The use of an acute stimulus in addition to basal sampling reduces the number of studies which are inconclusive because basal renal vein samples show little evidence of active renin secretion (Vaughan et al., 1973). In the present study eleven of the twenty-seven non-lateralizing studies showed a gradient between renal vein samples and peripheral renin in basal samples which was insufficient to account for the peripheral value at the time of sampling, according to the criteria of Vaughan et al. (1973), but symmetrical secretion was clearly demonstrated after diazoxide.

The use of intravenous diazoxide appears to be a safe, simple way of accentuating the distinction between lateralizing and non-lateralizing renal vein renin studies.

References


