Cushing, Cortisol, and Cardiovascular Disease
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Abstract—Cushing’s syndrome of glucocorticoid excess is named after the eminent Boston neurosurgeon Harvey W. Cushing (1869-1939). The recognition that glucocorticoid excess produces hypertension led to examination of the role of cortisol in essential hypertension, but it is only over the last decade that evidence has emerged to support the concept. Despite the widespread assumption that cortisol raises blood pressure as a consequence of renal sodium retention, there are few data consistent with the notion. Although it has a plethora of actions on brain, heart and blood vessels, kidney, and body fluid compartments, precisely how cortisol elevates blood pressure is unclear. Candidate mechanisms currently being examined include inhibition of the vasodilator nitric oxide system and increases in vasoconstrictor erythropoietin concentration. (Hypertension. 2000;36:912-916.)

Key Words: brain ■ glucocorticoids ■ hypertension, essential ■ cortisol ■ blood pressure

Harvey W. Cushing (1869-1939) was a neurosurgeon who made important contributions to the physiology and pathophysiology of the pituitary gland. He was a pioneer in neurosurgical techniques and he played a leading role in reducing mortality from brain surgery. He is best remembered today for his description of the condition that bears his name, the glucocorticoid excess syndrome. The eponym is less commonly used for acoustic neuroma. 1

Cushing was a neighbor of William Osler and subsequently won the Pulitzer Prize for his work, “A Life of Sir William Osler.” His descriptions of pituitary abnormalities were outlined in a monograph “The Pituitary Body and Its Disorders” in 1912, the year he became Professor of Surgery at Harvard and Surgeon in Chief at the Peter Bent Brigham Hospital.

Cushing once discussed Paris with a colleague, William McCalmont, and said to him “Let us meet at the top of the Eiffel Tower 10 years from now on July 4 at 2 in the afternoon and continue this conversation.” The incident was mentioned no more but at the appointed time, McCalmont went to Paris and to the top of the Eiffel Tower. He was unable to find Cushing but then noticed a small iron staircase, which went to the very top. There he was greeted by Cushing, saying, “Well, Willy, I almost despaired of you getting here.” 1

Cortisol and Essential Hypertension
Given the prominence of high blood pressure as a feature of Cushing’s syndrome, early studies examined the role of cortisol in essential hypertension but without finding abnormalities of cortisol secretion or concentration.2 More recently it has been recognized that cortisol may be involved in a number of forms of hypertension including apparent mineralocorticoid excess,3 licorice abuse,2 and chronic renal failure.4 Several rare syndromes of abnormal tissue sensitivity to glucocorticoids have been described, raising the possibility that abnormalities in tissue sensitivity to cortisol may be important in essential hypertension.

There are various lines of evidence supporting a role for cortisol in essential hypertension. Some years ago, we reported a placebo-controlled study in which blood pressure in a group (n = 8) of patients with essential hypertension was lowered by a small dose of dexamethasone (0.5 mg nocte [at night]) administered over a period of 4 weeks. The same dose had no effect on blood pressure in normotensive individuals.6 This study was compatible with the notion that the hypothalamic-pituitary axis was contributing to the hypertension in these patients (although not excluding a role for adrenocorticotrophin-dependent steroids other than cortisol). More recently, cross-sectional data from the Paris Prospective Study 1 showed elevated morning plasma cortisol levels in untreated hypertensive men, most particularly in a lean subgroup.7

Cortisol Metabolism
The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) acts as a tissue-specific protector of type I mineralocorticoid receptors in mineralocorticoid-responsive target tissues by exclusion of endogenous glucocorticoid, in particular by catalyzing the conversion of the biologically active cortisol to inactive cortisone. In the absence of this enzyme, tissues are exposed locally to excess cortisol; in the kidney, this produces sodium retention and hypertension. It has been assumed that the latter is consequent of the former, but as we discuss below, the association is not necessarily causal. Coding abnormalities in the enzyme lead to the syndrome of

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apparent mineralocorticoid excess, the features of which are due to cortisol, and it has been postulated that milder abnormalities of cortisol metabolism could contribute to essential hypertension by allowing exposure of the mineralocorticoid receptors to cortisol. Walker et al8 reported prolonged cortisol half-life in a subgroup of patients with essential hypertension, but the ratio of cortisol to cortisone in plasma and their metabolites in urine was normal. Cortisol half-life correlated with blood pressure. These results suggested a deficit in both 11β-HSD and also 11β-reductase activity, analogous to carbeneoxolone administration.8 Walker and his coworkers9 postulated that deficiency of 11β-HSD may allow increased exposure of mineralocorticoid receptors to glucocorticoids in extrarenal sites, particularly vascular smooth muscle and heart. In support of this notion, Brem and colleagues10 found a bidirectional NADP+-dependent 11β-HSD (ie, 11β-HSD1) in rat vascular smooth muscle.

Soro and coworkers11 have reported increased ratios of urinary cortisol to cortisone metabolites and increased 5α-to-5β-reductase metabolites in patients with untreated essential hypertension, consistent with reduced 11β-HSD and reduced 5β-reductase activities in essential hypertension. In another study, increased urinary free cortisol has been associated with salt-resistant essential hypertension.12

Endogenous Inhibitors
To determine whether endogenous inhibitors of 11β-HSD might contribute to essential hypertension,13,14 Takeda et al15 used urine extracts from hypertensive subjects to inhibit 11β-HSD2 in homogenized human kidney. Endogenous renal 11β-HSD–inhibitory factor was significantly increased in patients with low-renin essential hypertension, and urinary excretion of inhibitory factor(s) correlated with urinary sodium excretion, suggesting that sodium may influence the activity of 11β-HSD by modulating the endogenous renal 11β-HSD–inhibitory factor(s).15

Role of the Glucocorticoid Receptor
Observational studies suggest that variations in the glucocorticoid receptor (GR) gene may contribute to essential hypertension.16 Watt and coworkers17 studied a population of young people with contrasting familial predispositions to develop hypertension and found that homozygotes for the AA allele had higher blood pressure scores that those for the alternative aa allele, whereas heterozygotes were intermediate. Weaver et al18 found that the larger allele (A) was associated with severe hyperinsulinemic obesity, a feature seen in some patients with essential hypertension,16 as well as in Cushing’s syndrome, where it is a characteristic finding. However, Lin and coworkers19 were unable to find evidence for an association of the glucocorticoid receptor gene locus in essential hypertension.

Connell et al16 measured glucocorticoid receptor binding characteristics in circulating leukocytes and found a trend for lower receptor affinity in subjects homozygous for the A allele. Furthermore, they reported a trend for the inhibition of lysozyme production to be less sensitive to dexamethasone in AA homozygotes,16 whereas AA homozygotes had greater skin vasoconstrictor response to the topical budesonide. This discrepancy between the in vitro trend for reduced binding and in vivo evidence of increased steroid action in AA homozygotes was unexplained but might reflect ligand (dexamethasone versus budesonide) or tissue specificity.16 Mulatero et al20 also found impaired binding of cortisol to the glucocorticoid receptor in hypertensives, whereas Walker et al21–23 reported increased glucocorticoid sensitivity in subjects at risk for hypertension and cardiovascular disease and in essential hypertension.

Sensitivity to Cortisol
Walker et al23 found that patients with essential hypertension were more sensitive to topical glucocorticoids (both cortisol and beclomethasone) than were control subjects and that cortisol half-life was prolonged in the hypertensive subjects. In contrast, Mulatero et al20 reported reduced affinity of cortisol for the glucocorticoid receptor in leukocytes from patients with essential hypertension, and decreased sensitivity to cortisol appeared to be associated with renin suppression.

Neonatal Programming of Hypertension
There has been much interest in human epidemiological data, which suggest that programming of blood pressure may occur in utero. Low birth weight is linked with raised blood pressure in adult life. Phillips and coworkers24 investigated the relation between birth weight, fasting plasma cortisol concentrations, and current blood pressure in 3 populations (670 subjects). Low birth weight was associated with raised fasting plasma cortisol concentrations in all 3 populations, and fasting plasma cortisol concentrations correlated positively with current blood pressure. These data suggest increased activity of the hypothalamic-pituitary-adrenal axis may link low birth weight with raised blood pressure in adult life.

In the rat, placental 11β-HSD may protect the fetoplacental unit against the glucocorticoid effects of corticosterone,25,26 and variations in 11β-HSD activity may influence fetal growth and ultimately, blood pressure.25,27 In fetal sheep, exposure to cortisol in utero between 22 and 29 days of gestation leads to subsequent elevation of blood pressure in adult life.28

Mechanisms of Cortisol-Induced Hypertension
Role of Salt and Water Retention
It is still accepted by many that steroid hormones produce hypertension by acting through renal type I mineralocorticoid receptors to produce salt and water retention. This is not the case for synthetic glucocorticoids, for example, dexamethasone and prednisolone, which reproducingly elevate blood pressure despite their natriuretic effects,29 but is the generally accepted explanation for the hypertension produced by cortisol.30 The logic is that because cortisol produces renal sodium retention and hypertension, the relation is causal, but the evidence for this sequence of events is lacking (Table).31 Spironolactone at 400 mg/d completely prevented the salt and water retention produced by cortisol (80 mg/d) without affecting the increase in blood pressure.32 Montella-Waybill et al33 found that spironolactone did not affect cortisol-induced (240 mg/d) sodium retention or rise in blood pressure...
but did prevent the reduction in serum potassium. They had previously found that spironolactone partially reversed the sodium retention of cortisol at 120 mg/d, although the interpretation of the study was complicated by weight loss and negative sodium balance. The data are consistent with dissociation between sodium retention and blood pressure–raising effects of cortisol. They are also consistent with the notion that cortisol at a lower dose produces sodium retention through a type I receptor–mediated mechanism blocked by spironolactone, but at higher cortisol concentrations there is downregulation of type I receptors, and sodium retention reflects other mechanisms.

Whether a causal relation between renal sodium retention and hypertension even holds true for adrenocortical steroids with predominant mineralocorticoid activity, such as aldosterone, is also questionable. Whereas cortisol, aldosterone, and low-dose 9α-fluorocortisol all produce a rapid antinatriuresis in humans, cortisol elevates blood pressure within 24 hours, but no such rise is seen with the mineralocorticoids, compatible with classic descriptions of the different time course of glucocorticoid and mineralocorticoid hypertension.34 Twenty years ago, Bohr35 proposed that central mineralocorticoid effects of deoxycorticosterone were important in its blood pressure–raising actions. Subsequently, in a series of elegant studies, Gomez-Sanchez36,37 has shown that experimental aldosterone hypertension relates to central rather than peripheral action of aldosterone and that pressor effects of aldosterone are distinct from mineralocorticoid-mediated changes in fluid and electrolyte balance, increase in salt appetite, increase in vascular reactivity, and trophic effects on the vessels and heart. In contrast, central glucocorticoid administration lowers blood pressure and central glucocorticoid antagonists raise blood pressure.38,39

If glucocorticoid-induced hypertension, and in particular, cortisol-induced hypertension, is not a consequence of activation of renal type I mineralocorticoid receptors, can it be explained by activation of classic type II glucocorticoid receptors? Clore et al40 found that the glucocorticoid antagonist RU-486 did not modify cortisol-induced elevations in blood pressure despite blockade of cortisol-induced hyperinsulinemia. In experimental studies of ACTH-induced hypertension in the rat (which is a consequence of ACTH-induced secretion of the major rat glucocorticoid corticosterone), we have shown that neither spironolactone at a dose that inhibits sodium retention nor RU-486 at a dose that inhibits metabolic glucocorticoid effects has any effect on the rise in blood pressure.41 Thus, the hypertension produced by the major naturally occurring glucocorticoids is not simply explained through classic steroid actions.

The mechanism(s) by which cortisol raises blood pressure in humans is unclear. Cardiac output is increased, but this is not essential for the rise in blood pressure,42 and sympathetic activity is decreased.43–45 Cortisol has a variety of effects on kidneys, heart, brain, blood vessels, and body fluid volumes, but it is not clear which of these are causal rather than epiphenomena or amplifiers or modulators of the rise in blood pressure.

Current interest focuses on vascular effects of cortisol and the role of the nitric oxide (NO) system.46 Glucocorticoids have a variety of effects on the NO system, including inhibition of iNOS and eNOS isoforms, inhibition of transmembrane arginine transport, and inhibition of synthesis of the NO synthase cofactor tetrahydrobiopterin.47–49 A role for the NO system in cortisol-induced hypertension was suggested by studies in the rat, in which l-arginine prevented the development of ACTH-induced hypertension50 and by studies in normal subjects on a restricted nitrate diet.51 Cortisol increased blood pressure in association with reductions in plasma nitrate/nitrite concentrations, but there was no

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**Forearm blood flow (FBF) responses to increasing doses of acetylcholine (ACh) and sodium nitroprusside (SNP) on day 5 of placebo (●) and cortisol (▲) treatments before LNMMA (closed symbols) and after LNMMA (open symbols). Area under dose-response curves between placebo and cortisol treatments to both ACh and SNP were compared before and after LNMMA in placebo-treated subjects (*P<0.05); dilator response to ACh was attenuated after 5 days of cortisol compared with placebo (#P<0.05).**
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change in plasma arginine or symmetric or asymmetric dimethyl arginine, indicating that the reductions in nitrate could not be explained by changes in substrate availability or endogenous NO synthase inhibitors. More recently, using bilateral forearm plethysmography, we have found impaired cholinergic vasodilation after cortisol administration (Figure). Cortisol did not affect the response to sodium nitroprusside, and although \( N \)-monomethyl-L-arginine inhibited cholinergic vasodilation in placebo-treated subjects, it had no additional effect in the presence of cortisol (Figure). Taken together, these results are consistent with a role for abnormalities of the NO system in cortisol-induced hypertension, and we are currently examining various components of the system to better define the abnormality.

We have also investigated the possible role of erythropoietin (EPO) as a mediator of cortisol-induced hypertension in healthy men. EPO concentrations correlate with blood pressure in patients with essential hypertension, and direct vasoconstrictor effects of EPO have been shown in vitro. EPO-induced hypertension appears to be in part due to NO resistance, and polycythemia is a well-recognized complication of chronic glucocorticoid excess. Accordingly, EPO might play a role in glucocorticoid hypertension. Cortisol increased both blood pressure and serum EPO concentrations, and with 200 mg/d cortisol there was a positive correlation between the change in systolic blood pressure and the change in EPO concentration. It is possible that the rise in EPO concentration occurs as a consequence of some physiological effect of cortisol such as increased renal vascular resistance, but the mechanism is unknown and there are currently no data on the role of EPO in chronic glucocorticoid excess. Similarly, whether EPO plays a pathogenic or bystander role in hypertension is unresolved.

In summary, cortisol has a range of effects on cardiovascular regulation. Which of these effects are causal in cortisol-induced hypertension remains to be determined.

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References


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