Editorial Commentary

Long Renal Arteries
Too Much of a Good Thing?

Myron H. Weinberger

It has now been >100 years since the seminal observations of Professor Tigerstedt and his medical student—colleague, Bergmann, demonstrated the pressor effects of renal extracts. The clinical relevance of these observations became more apparent with the classical experiments of Harry Goldblatt and his colleagues who demonstrated in the 1930s that inducing renal ischemia by ligation of a renal artery could cause hypertension in dogs. The identification of renin and angiotensin in the laboratories of Page and Helmer in Indianapolis and, virtually simultaneously, by Braun-Menendez and Fasciolo in Buenos Aires, Argentina, elucidated the mechanism involved.

The search for human counterparts of the experimental paradigm by which renal ischemia led to hypertension and its potential remediation soon followed with the application of the tedious biological assay for renin to venous blood samples obtained from the kidneys with stenotic lesions in vivo by Judson and Helmer. This introduced an era, encompassing the past 40 years, when the possibility of correcting this increasingly recognized secondary form of hypertension became feasible. A variety of techniques have now been devised to detect abnormalities of renal blood flow and to attempt to correct them by surgical means or with a variety of vascular interventions when found.

Although ischemic lesions of the main renal artery have received the overwhelming majority of attention, other forms of renal ischemia resulting in hypertension have also been identified. Page created an experimental form of hypertension in dogs by inducing perinephritis as a result of encasing the kidney in cellophane. A human counterpart of this identifiable form of hypertension caused by post-traumatic perinephric hematoma and resulting fibrosis, the "Page" kidney, has also been shown to be renin-dependent and responsive to removal of the damaged kidney. Reports of many renin-secreting tumors of a wide variety of causes have appeared since the initial one, often with resolution of the hypertension on removal of the affected kidney. Another uncommon renal abnormality associated with hypertension and hypersecretion of renin is the Ask-Upmark kidney, thought to result from partial amputation of the kidney as the result of infection, trauma, or of idiopathic origin. Whereas this has typically been identified in childhood, we have encountered several adults who appear to have this structural abnormality of the kidney, increased production of renin from the renal vein blood of the involved kidney, and a reduction of blood pressure with administration of antihypertensive agents known to reduce or block the renin-angiotensin system (β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers). In this issue of Hypertension, Kem et al add another, less common, renin-dependent form of potentially remediable hypertension to the list of renal disorders, that apparently resulting from an elongated and aberrant accessory renal vessel.9

This new report describes the findings in 2 young subjects in whom a diligent search for an explanation of their hypertension led the investigators to the kidneys. Instead of finding a vascular abnormality of the main renal artery, such as that caused by fibromuscular hyperplasia or external compression of the renal artery by a neurofibroma or similar lesion, evidence of structural abnormality of the kidney, such as the "Page" or "Ask-Upmark" lesion, or evidence of a renin-secreting tumor, their persistent search revealed increased renin concentration from the venous drainage of a renal segment supplied by an accessory renal artery that was elongated and/or "aberrant." In both subjects described, the blood pressure appeared to respond to drugs that would be expected to be most effective in renin-dependent forms of hypertension and, in one case, to subsequent partial nephrectomy involving the segment supplied by the aberrant vessel. The authors offer a rheological explanation for the process whereby the renal ischemia ensued. Although it would have been reassuring to observe cytoimmunochemical confirmation of the enhanced juxtaglomerular cell activity in the involved tissue compared with nearby tissue in the removed segment, there is much more to be learned from this report than simply another rare form of hypertension. How were these lesions identified?

One of the obvious clues that led the investigators to aggressively search for a possible cause of the hypertension came from the young age of the subjects and another came from the severe elevation of blood pressure. Despite the fact that essential hypertension has been encountered more frequently among children and adolescents in recent decades than ever before, the discovery of substantial hypertension in a young person should trigger strong consideration of a secondary or identifiable cause. In addition to exogenous etiologies for hypertension in young people, the kidneys are often found to be responsible. How far should one pursue this possibility? Obviously, studies of renal blood flow and

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anatomy are required to identify possible renal causes of hypertension. In these 2 cases, subtle abnormalities of these initial studies led to attempted confirmation by obtaining segmental renal venous samples for renin determination. This is often more complex than it might initially seem since congenital variability in the genitourinary tract is very common as noted by the authors, particularly with respect to multiplicity of the renal vasculature. Moreover, there is not consistent pairing of duplicated renal arteries and renal veins, particularly as they supply and drain segments of the renal tissue. Thus one cannot always assume that the venous sample derived from a segmental renal vein necessarily drains the same segment supplied by a similar segmental or accessory renal artery. It is also important to use a stimulatory maneuver, such as diuretic and angiotensin-converting enzyme inhibitor treatment as the authors did, often enhanced by tilting, to maximize renin secretion by the ischemic segment.

Another clue to a possible renal source for the hypertension in these subjects came from a less frequently considered observation. Both subjects had samples of peripheral blood obtained for measurement of plasma renin activity and plasma aldosterone, ostensibly to rule out the possibility that the hypertension was the result of excessive aldosterone production by the adrenal. Rather than finding an increased aldosterone-to-renin ratio typical of primary aldosteronism, both patients demonstrated what appeared to have been an abnormally low ratio, suggesting an excess of renin in relation to aldosterone. Unfortunately, follow-up assessment of this ratio after partial nephrectomy in the single subject was not reported. Whereas this end of the aldosterone-to-renin ratio has not been actively investigated as a screening technique for renin-dependent forms of hypertension, it will be interesting to see whether this has any usefulness in the future.

References
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