Accessory Renal Arteries—Mostly, But Not Always, Innocuous

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Since the classical observation of Harry Goldblatt (1), hyperreninism resulting from renal ischemia has become an established paradigm to explain several forms of hypertension. The closest human counterparts to the experimental model of Goldblatt are the various forms of renal artery stenosis, fibromuscular or atherosclerotic. The clinical diagnosis is based on the combination of an activated renin-angiotensin system and morphologic evidence of a hemodynamically relevant arterial stenosis, ideally supplemented by evidence of deficient renal perfusion (2–4). Accessory renal arteries have been known since the early days of human autopsy. It has been reported that they occur in 26% of individuals (5) and originate mostly directly from the aorta (6). Their frequency reflects the complexity of the organogenesis of the kidney: They represent vestiges of the ascent of the kidneys during the 6th to 9th weeks of gestation from the pelvis to the final lumbar location. This movement is accompanied by sequential sprouting of branches from the aorta while the preceding lower branches disappear. Nevertheless, it remains puzzling why this is infrequent in rats (I haven’t seen a single case in a great number of rats on which I operated).

After the report of Marshall (7), there have been numerous claims in the literature that accessory renal arteries increase the risk of hypertension (7–13). The death knell to this hypothesis seemed to be the study of Gupta and Tello (6), who studied 185 hypertensive patients using magnetic resonance angiography. They found that the risk to find a renal artery stenosis in an individual with an accessory artery as compared with an individual with a single renal artery was not significantly different. This observation is undoubtedly correct, but the beauty of medicine is that there is no rule without an occasional exception.

In this context several authors referred to the successful surgical treatment of renal hypertension in children, but this concerned partial nephrectomy when lesions of intrarenal vessels associated with segmental hypoplasia (Ask-Upmark), reflux nephropathy, or arteriovenous malformations (14)—quite unrelated to the topic under discussion here.

In the distant past, Györi (15) had postulated that supernumerary renal arteries were more prone to develop stenosing lesions and, more importantly, he also speculated that they are longer and their calibre is smaller than the main arterial trunk, thus raising resistance and potentially predisposing to underperfusion according to the law of Hagen-Poiseuille. This hypothesis had prompted Glodny et al. (16) to study 62 consecutive patients who had undergone angiography for various reasons. The kidneys were supplied by 2 single arteries in 29 patients and by multiple renal arteries in 33 patients. Before stimulation, the plasma renin was significantly higher ($P < 0.0127$) in the latter group (1.73 ± 0.38 ng angiotensin I/ml per min versus 0.79 ± 0.13 ng angiotensin I/ml per min); 60 min after stimulation the respective values were $3.7 ± 0.50$ versus $2.59 ± 0.4$. The authors concluded that an activated renin system contributed to the BP elevation in these patients, but these observational data failed to prove a causal relationship.

The paper of Kem et al. (17) is remarkable because it went beyond these reports and provided proof for an activated renin system by documenting an activated renin system before and normalization of BP after resection of the nonstenosed but narrow accessory artery with partial nephrectomy. A 5-yr-old boy with severe hypertension had no stenosis of renal vessels but also had an elongated, nonstenosed, aberrant artery arising from the common iliac artery near the aortic bifurcation feeding the lower pole of the right kidney. The renal vein renin ratio (right/left) was 2:1 in the recumbent position (to exclude ptosis of the kidney). By ultrasonography there was a difference in kidney size (right kidney, $9.4 \times 3.5$ cm; left kidney, $8.8 \times 3.8$ cm). The basal ratio of plasma aldosterone/plasma renin
activity (PA ng/dl; PRA ng/ml per h) was relatively low at 1.8:1, but increased to 4.3:1 after administration of captopril accompanied by a significant decrease in BP. Partial nephrectomy yielded tissue which showed fibrosis and focal sclerosis of glomeruli, presumably indicators of intermittent ischemia. Postoperatively his BP had decreased to 120/70 mmHg off medication. A less well-documented second case was reported as well.

This case should not prompt indiscriminate interventions in hypertensive patients with accessory renal arteries. It should alert physicians, however, to the possibility, admittedly remote, of the occasional causal role of accessory renal arteries in patients with severe and difficult to manage hypertension. For several reasons this possibility may be greater in children.

References
Where Does Some of the Ingested Sodium Chloride Hide without Exerting Osmotic Pressure?


In the beginning the abundance of the sea
Led to profligacy
The ascent through the brackish waters of the estuary
To the salt-poor lakes and ponds
Made immense demands
Upon the glands
Salt must be saved, water is free.
(Maurice B. Strauss, Boston)

Since the introduction of the brilliant concept of Claude Bernard that the body comprises two distinct compartments the “milieu interieur” and the “milieu exterieur,” the partitioning between the two had been a challenge to the investigators. As Homer W. Smith pointed out and as beautifully described by the above sonnet, the transition from the salty sea to dry land created an enormous challenge to sodium homeostasis because of the need to preserve the precious sodium ion.

Which mechanisms underlie sodium homeostasis? The early studies got it approximately right—but as we know today only approximately, and the early investigators had cautiously pointed to the limitations of their findings (1): The paradigm was that sodium is restricted mainly to the extracellular fluid and potassium to the intracellular space. The disequilibrium across the cellular membrane is maintained by the Na⁺,K⁺ATPase. The constancy of the extracellular space is mainly, but not exclusively, the task of mineralocorticoid activity. Unlimited sodium retention is prevented by the “safety valve” of the escape phenomenon, i.e., the onset of natriuresis despite persistently high mineralocorticoid activity when a hypothetical limiting size of the extracellular space has been transgressed.

Needless to say, the regulation of the intravascular and extracellular spaces is of considerable clinical importance, given the disturbances of whole body sodium in congestive heart failure, nephrotic and nephritic syndrome, renal failure, and others.

We have learned in physics that theories that explain findings satisfactorily (like the Maxwell equations) may break down when one goes to more extreme conditions and increases the precision of the measurements.

Similarly, the careful and laborious studies of Titze *et al.* (2–5) shatter some firmly held beliefs, i.e., that sodium is restricted to the extracellular space and that it is retained only with a commensurate amount of water to maintain isosmolality. Of course, there had been pointers to this in the past, but the precise measurements and data had to wait for the above investigations.

The aforementioned study by Titze *et al.* (2) addressed the issue whether, under the influence of mineralocorticoids (deoxycorticosterone-acetate, DOCA), sodium and water are retained in isomotic proportions, in other words 1 L water per 9 g NaCl; and, if not, where the sodium that had failed to retain water had gone.

To this end the authors examined female Sprague-Dawley rats receiving tap water or 1% saline as drinking fluid. These were compared with female Sprague-Dawley rats that had received subcutaneous DOCA pellets and were also kept on tap water or 1% saline.

The salient results of this 5-wk study are the following: Despite considerable retention of sodium (0.255 ± 0.022 on DOCA compared with 0.170 ± 0.010 mmol/g dry weight without DOCA), the retention of water was only moderate and less than what was calculated assuming that water was retained to maintain isosmolality (0.685 ± 0.119 ml water/g wet weight on DOCA compared with 0.648 ± 0.130 ml water/g wet weight without DOCA). The calculation
showed that 4.75 mmol Na\(^+\) had been retained, which should have caused the retention of 32 ml water. But only 7.75 ml water were detected, leading to the conclusion that 75 to 80% of the retained sodium was retained in an osmotically inactive form.

This finding leads to the obvious question: Where does the sodium go? Tissues were subjected to desiccation and ashing to measure their electrolyte composition. In muscle, substantial amounts of sodium were retained (0.220 \(\pm\) 0.029 ml water/g dry weight on DOCA compared with 0.145 \(\pm\) 0.021 mmol/g dry weight without DOCA). This was associated with loss of potassium, suggesting that an isosmotic neutral exchange of K\(^+\) for Na\(^+\) had taken place; in other words osmotically neutral Na\(^+\) retention had occurred and was balanced by K\(^+\) loss.

Although past studies had documented that the skin could indeed store sodium in an osmotically inactive form, the contribution of skin storage, although significant, was not so spectacular; in contrast to what had been seen in muscle it was not balanced by a K\(^+\) loss. This implies that there must have been osmotically inactive Na\(^+\) storage by another mechanism, e.g., by binding to glycosaminoglycans (3).

Are these findings in line with previous observations? Indeed, balance studies in humans had documented that administration of sodium chloride did not invariably lead to volume retention (6–8). Conversely, it had also been observed that sodium loss is not necessarily paralleled by volume loss (9). The imbalance between sodium retention and water retention, pointing to “hidden” sodium stores, is particularly pronounced in patients with cardiac edema (10).

Retention of more sodium than accounted for by the increase in the extracellular space had also been shown in the DOCA-salt model of the dog (11), and an increase in muscle sodium had been reported in DOCA rats (12,13).

Though many mechanistic details await clarification, the obvious question is whether the findings have clinical implications. The classic concept that the BP increase induced by a positive sodium balance is simply explained by hypervolemia and a delayed autoregulatory increase of peripheral vascular resistance (14,15) requires reassessment and inclusion of complementary mechanisms, because direct uptake of sodium by vascular smooth muscle cells might well have a volume-independent hypertensinogenic effect. This might be particularly relevant in patients with impaired or absent renal function, where the BP-raising effect of a positive sodium balance is particularly pronounced (16,17).

Another relevant issue is the sodium retention in cardiac (10) and nephrotic edema (18), which again require reassessment in the light of the above findings.

Finally, as pointed out by the authors, the quantitative algorithms considered for the treatment of dysnatremias (19) might require modification as well.

References
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Cardiovascular Effects of Secondhand Smoke Nearly as Large as Those of Smoking—and How about Renal Effects?

Cardiovascular Effects of Secondhand Smoke: Nearly as Large as Smoking, Am Heart J 111: 2684–2698, 2005

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One of the most remarkable achievements of nephrology in recent decades was the observation that progression of renal disease is susceptible to intervention. Although the efficacy of intervention, particularly by lowering blood pressure (1) and by blockade of the renin-angiotensin system (2–4), has been proven in controlled trials, the long-term outcomes are not fully satisfactory (5). The answer may well be the combination of different types of intervention (6), a strategy that has been immensely successful in diabetes (7). A complementary approach is the elimination of additional insults to the kidney, e.g., cessation of smoking (8), avoidance of nonsteroidal anti-inflammatory agents (9) or of acetaminophen, aspirin, and other analgesics (10)—although harm by the latter agents has not been universally confirmed.

In diabetic patients, the adverse renal effects of smoking were observed 27 years ago (11) and observational studies suggested that cessation of smoking attenuated the progression of diabetic nephropathy (12). These observations in diabetic patients went largely unnoticed by the renal community, however, until solid evidence was provided by a retrospective case-control study which showed that the risk of end-stage renal disease in nondiabetic patients with primary renal diseases (i.e., IgA glomerulonephritis or polycystic renal disease) was significantly higher in smokers, at least in male smokers (13). More recently, several studies confirmed this finding (14,15) and some authors documented deterioration of renal function even in patients without primary renal disease, e.g., severe hypertension (16), advanced age (17) and others. A high
proportion of smokers is found among microalbuminuric subjects (18–20) and a prospective study in the general population found that current cigarette smoking increased the relative risk of chronic kidney disease (CKD) by a factor of 2.9 in women and 2.4 in men. Cigarette smoking accounted for 31% of the attributable risk of CKD (21). Because of these and other data, it has been recommended that individuals with CKD should be strongly advised to stop smoking (8).

But is this good enough? The above scholarly paper by Barnoya and Glantz (22) marshals the evidence that the effect of passive smoking on cardiovascular risk is surprisingly strong and quantitatively comes close to that of active smoking. Some background information on passive smoking may be useful. Great concern about health hazards from passive smoking had originally been raised by the study of Hirayama (23), who had noted an excess frequency of bronchial carcinoma in nonsmoking Japanese wives married to smoking husbands. This finding helped create awareness that environmental tobacco smoke can harm nonsmokers (24). This finding is hardly surprising: Not only the mainstream smoke, which is inhaled and exhaled by the smoker, but also the sidestream smoke contains numerous substances (actually >4000 substances in sidestream smoke, of which 50 are known carcinogens) (25). The composition differs from mainstream smoke and is in some respects even more alarming (26). The main forms of passive exposure to smoke are the working place, the home and—somewhat less important quantitatively—restaurants/bars and public transportation (27). As recently described in detail by Diethelm et al., the high risk of sidestream smoke had apparently been known to the industry, particularly Philip Morris USA, for a long time (26). To conceal access to the primary experimental data, a sophisticated structure of secret transfer of experimental data had been arranged and what had been published was apparently manipulated by industry (28). There is not only clear evidence in the meta-analysis of Boffetta (29) that individuals exposed to passive smoke more frequently have bronchial carcinoma with a relative risk of 1.25 (95% confidence interval [CI] 1.15 to 1.37). The authors also found a definite dose-response relationship, the odds ratio for the highest exposure group being 2.8 (1.6 to 4.8) (30).

But apart from these known risks of carcinoma and pulmonary disease, there is now also incontrovertible evidence for a high cardiovascular risk of passive smoking as summarized in the above meta-analysis of Barnoya (22), which included the results of 29 studies. Using a random effects model, the author computed the pooled relative risk of ischemic heart disease: In never smokers exposed to second-hand smoke relative to the risk in individuals not exposed to second-hand smoke, the risk estimate was 1.31 (95% CI 1.21 to 1.41)—more than one would expect, based on the known risk associated with active smoking and the relative doses of tobacco smoke delivered to smokers and nonsmokers.

For several reasons this observation is bad news for renal patients. First, even minor renal dysfunction causes a dramatic increase of cardiovascular risk (31–33) and for obvious reasons any additional risk is most undesirable. Second, however, the suspected pathomechanisms by which passive smoking causes vascular lesions and raises cardiovascular risk are likely to play a role in the genesis of the predominantly vascular lesions underlying progression of renal disease in smokers. Although studies on the acute effects of smoking in occasional smokers with renal disease found an acute increase in albumin excretion (34), histological evaluation of renal biopsies in patients with primary renal disease showed evidence of pronounced vascular lesions in smokers compared to nonsmokers, i.e., significantly more marked myointimal hyperplasia and a trend for more severe arteriolar lesions (35). This observation is in line with functional studies in chronic smokers, which documented reduced renal plasma flow despite maintained GFR, accompanied by increased plasma endothelin concentrations as putative evidence of endothelial cell dysfunction (14).

What is the evidence for platelet activation, endothelial dysfunction, oxidative stress, and inflammation by second-hand smoke? As soon as 20 minutes after exposure of nonsmokers to second-hand smoke, platelets were activated to the point that they were no longer discernibly different from platelets of smokers (36). This observation is in line with the study of Rubenstein et al. (37): Extracts from sidestream smoke activated platelets more potently than extracts from mainstream smoke. Furthermore, thromboxane and other markers of platelet activation are
significantly increased in passive smokers (38). Evidence of endothelial cell dysfunction is provided by observations that, within minutes after exposure to second-hand smoke, endothelium-dependent vasodilatation (39) and coronary flow reserve (40) are reduced. This is accompanied by decreased endothelial nitric oxide (41). Second-hand smoke causes oxidative stress (42) and leads to antioxidant depletion such as decreased vitamin C (43), β-carotene (44), and folate (45) concentrations. This is accompanied by increased plasma 8-hydroxy-2-deoxyguanosine concentrations (46) as evidence of oxidant DNA damage and by a compensatory increase in enzymes breaking down reactive oxidant species such as superoxide dismutase or glutathione peroxidase. Finally, the evidence of inflammation triggered by second-hand smoke comprises increased acute phase proteins (47), fibrinogen (48), activation of neutrophils (49), and others.

The obvious question raised by the above findings is this: Should we advise renal patients not only to stop smoking but also to try to avoid passive exposure to cigarette smoke? Although none of the textbooks mentions this, I think the answer should be yes and I hope that the above arguments convince other nephrologists as well.

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