Lowering of Blood Pressure—The Lower, the Better?

Dogma Disputed: Can Aggressively Lowering Blood Pressure in Hypertensive Patients with Coronary Artery Disease Be Dangerous?


Blood pressure (BP) control is a major issue in nephrology, both in the predialysis phase of chronic kidney disease (CKD) and—more complex and controversial—while patients are on dialysis (1–7). There is no doubt that in renal patients hypertension aggravates progression and contributes to cardiovascular death. The percentage of patients reaching recommended target BP values suggested by the guidelines (8) is soberingly low in renal patients (9,10) as is also the case in diabetic patients (11).

In CKD patients, nephrologists must be concerned not only whether BP is too high, but also whether BP may actually become too low. For instance, in a controlled prospective trial on type 2 diabetic patients with advanced nephropathy, Pohl et al. (12) noted that all-cause mortality was higher in patients with achieved systolic BP <120 mmHg, although progression was lowest at this level of BP. The authors could not decide whether low BP characterized patients with cardiac disease and the resulting high risk of cardiac death or whether mortality was the consequence of overly aggressive lowering of BP.

In patients on hemodialysis, several observational studies paradoxically showed that mortality was highest in patients with low predialysis or postdialysis BP values (13,14), particularly in the presence of high pulse pressure (15,16), although the importance of the association between low BP and mortality diminishes progressively with time on dialysis, possibly indicating that high-risk patients presumably suffering from cardiac disease die off as time goes by. The inverse relationship between BP and survival has been termed “reverse epidemiology” (17), explained by the confounding existence of the inflammation-malnutrition complex. Although such a causal relationship remains unproven, this gives another twist to the issue of what BP level is optimal in renal patients, particularly on hemodialysis.

Nearly 20 years ago Cruickshank and colleagues (18,19) had introduced the concept of a J-curve: Cruickshank et al. acknowledged that lowering BP reduced cardiovascular death. But they argued that after a nadir of cardiac mortality had been reached mortality increased again with decreasing diastolic pressure. The authors felt that this was due to compromised coronary perfusion. One argument for this hypothesis is the fact that coronary perfusion occurs exclusively during diastole, so low diastolic pressures would be particularly injurious to coronary blood flow. Despite some observations that were in agreement with this hypothesis (20), this concept had remained controversial. Obviously a J-curve must exist, as suggested a priori by the consideration that as BP approaches the value of zero survival becomes uncomfortably low. The crucial question therefore is whether an inflection point exists, at least in some patients, at BP within the range of values commonly achieved during treatment of hypertensive patients.

Throughout the years there has been little solid evidence to support the J-curve concept. For instance, in the Hypertension Optimal Treatment (HOT) study there was no convincing evidence that mortality was higher in patients achieving lower diastolic BP levels, although with foresight Kaplan had remarked that a “J-curve had not been burned off by HOT” (21). The discussion for and against had been simmering for years (22–25). The need for solid controlled evidence persisted, although the meta-analysis of Farnett et al. (25) had shown already that there was no consistent J-shaped relationship between stroke and diastolic pressure, while there was a consistent relationship between cardiac events and diastolic pressure. This meta-analysis has now been confirmed by the recently published post hoc analysis of Messerli et al. (26), which is based on the data of the International Verapamil-Trandolapril Study (INVEST) (27). The INVEST trial was a prospective, open-label, blinded end point trial (PROBE design). Patients with hypertension and coronary artery disease (n = 22,576) were randomized to receive a
calcium channel blocker (Verapamil)– or β blocker (Atenolol)–based antihypertensive strategy. Trandolapril or hydrochlorothiazide, respectively, were used as back-up therapy to achieve the goal BP values proposed by the Joint National Committee (JNC VI) (28), i.e., <140/90 mmHg and <130/85 mmHg for patients with diabetes or renal impairment. This goal had virtually never been achieved in such populations before, so that it had been impossible to assess the impact of very low diastolic pressures. The primary end point was all-cause death, nonfatal myocardial infarction, or nonfatal stroke. The study had proven that the Verapamil-based strategy was as effective as the conventional Atenolol-based strategy.

In the present post hoc analysis, Messerli et al. makes a robust case that, at least in these patients with pre-existing cardiac disease, a nadir of diastolic pressure did indeed exist for cardiac but not for cerebrovascular events. It also identified a history of coronary revascularization as a condition that predisposed to a lower risk of primary outcome, suggesting that coronary repair rendered the heart less susceptible to ischemia at low diastolic pressure. The finding of Messerli et al. concerning the importance of the diastolic pressure is in line with the observation of Owens and O’Brien that cardiac ischemic events are more related to diastolic than to systolic events (29). The analysis was based on a robust database of 2269 outcome events over a total of 61,835 patient years. The frequency of the primary outcome was related in a J-shaped pattern both to systolic and diastolic pressure, but the curve was relatively shallow for systolic pressure. In contrast, diastolic BP <60 mmHg increased the risk of a primary outcome by a factor of 3. This finding cannot be entirely attributed to an increase in systolic pressure with falling diastolic pressure as a result of aortic stiffening with consecutive widening of pulse pressure. Against this idea is the observation that the systolic BP was also lower in patients with low diastolic pressure, although proportionally less so. Nevertheless, when pulse pressure was added to the diastolic pressure model, pulse pressure was also associated with the primary outcome, as had previously been noted in the Framingham cohort (30). The nadir of primary outcomes was seen at a BP of 119/84 mmHg (unadjusted) and 129/74 mmHg (adjusted), respectively, quite similar to the nadir of 138.5/82.6 mmHg found in the HOT trial (31).

While at higher BP values the ratio myocardial infarction to stroke remained relatively constant, the ratio increased with a progressive decrease of diastolic pressure; one explanation might be that with lower diastolic pressure the frequency of myocardial infarction increases (possibly as a result of coronary underperfusion, although interpretation in terms of causality is a delicate issue), while the relative frequency of stroke does not. The latter is in line with the observation that the risk of stroke is exquisitely sensitive to the level BP (32).

This observation in patients with cardiac disease obviously must not be generalized and extrapolated to patients without cardiac disease, but in high-risk populations of coronary artery disease, e.g., in renal patients who have a high burden of coronary artery disease (33) and the additional burdens of cardiac microvascular disease (34,35) and endothelial cell dysfunction with reduced NO-dependent vasodilatation (36,37), the conclusion of Messerli et al. (26) is highly relevant, i.e., that “patients with occlusive coronary artery disease are put at risk of coronary events if diastolic pressure is low”, similar to what JNC VII had suggested (38).

In the context of hemodialysis, the issue arises of how safe it is to abruptly reduce volume excess and activate counterregulation via sympathetic and renin-angiotensin systems, particularly if BP is abruptly lowered as well (39). In hemodialyzed type 2 diabetic patients we found that the risk to die from myocardial infarction was 2.8-fold higher if a decrease of BP below the autoregulatory threshold of the coronaries of 80 mmHg occurred two or more times per week (40). Avoidance of such abrupt BP decreases may underlie, among other causes, the apparent survival advantage of long, slow dialysis procedures (1). The analysis of Messerli et al. forces one also to abandon the Communist idea that one BP on treatment is good for all patients, particularly hemodialyzed patients, as so often in medicine an individualized approach is superior to the clumsy “one BP for all” approach, considering above all the presence of coronary heart disease, diastolic pressure and pulse pressure, circadian BP profile, orthostatic BP stability, and many other aspects.
References
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Does Malfunction of Arachidonic Acid Epoxygenase Explain Salt-Sensitive Hypertension?

Salt-Sensitive Hypertension Is Associated with Dysfunctional Cyp4a10 Gene and Kidney Epithelial Sodium Channel.

Historians claim that the relation between high salt intake and high BP was known even to the ancient Chinese, as exemplified by the writings of the Yellow Emperor (1): “hence if too much salt is used in food, the pulse hardens, tears make their appearance and the complexion changes. . . .”. But it was the experiment of controlled sodium chloride loading by Ambard and Beaujard (2) that provided the first evidence of a link between salt loading and BP. The groundbreaking work of A. Guyton led to the modern concept that a disturbed BP/natriuresis relationship underlies any form of hypertension (3,4), i.e., that kidney malfunction—not necessarily primary kidney disease—is the reason why higher BP values are required to get rid of the dietary intake of sodium. Clinical studies documented that at least a proportion of patients with primary hypertension are “salt sensitive” (5), but even today there is no consensus on the method to identify “salt sensitivity.”

The finding that practically all monogenetic forms of hypertension are associated with increased renal tubular sodium reabsorption (6–8) immediately made tubular sodium transporters hot candidates for the genetic predisposition of the garden variety of primary hypertension, which is presumably polygenetic; so far the yield of these studies had been underwhelming. Although there is also some evidence for abnormalities of proximal tubular handling of sodium in primary hypertension (9), one particularly attractive candidate was ENaC (epithelial sodium channel), the epithelial cell sodium transporter in the most distal part of the nephron, the collecting duct, where the fine tuning of urinary sodium excretion is thought to take place. But primary hypertension stubbornly refused all efforts to link it to mutations of the ENaC analogous to the mutation of which had been found in the rare Liddle syndrome (10). Nevertheless, the concept to link primary hypertension, or at least the salt-sensitive varieties of primary hypertension, to ENaC malfunction appeared a priori plausible. Apart from direct mutations in the ENaC molecule, mutations coding for molecules modulating ENaC activity remained a possibility and it is here where the above authors struck gold.

The authors had previously shown that mice with disruption of the CYP4a14 gene develop androgen-sensitive hypertension and formation of the prohypertensive 20-hydroxyarachidonate (11). After previous suggestions by McGiff (12), Nakagawa et al. had concluded that Cyp4a arachidonate monooxygenase plays a role in the renal regulation of BP.

At this point it is necessary to digress for a moment for some comments on arachidonic acid metabolism. Arachidonic acid is metabolized by a group of cytochrome P450 (CYP; http://www.cypalleles.ki.se/) epoxygenases and ω-hydroxylases, which generate epoxyeicosatrienoic acids (EET) and 20-hydroxyeicosatetraenoic acid (20-HETE). In this study Nakagawa et al. had produced mice with disruption of cytochrome P450 family 4, subfamily a, polypeptide 10 (Cyp4a10−/−) (13). These mice developed normally and showed no evidence of organ malformation or disease. The phenotype was characterized by salt-sensitive hypertension, high salt intake causing sodium retention and fluid expansion (by nuclear magnetic resonance measurements); renal morphology and gross renal function were normal before and after salt loading. The knockout animals were normotensive on 0.05% salt (low salt), though in the knockout (both male and female), but not in the wild-type animals, BP increased substantially when they were switched to 0.3% (normal salt) and 8% (high salt), respectively.

How did the disruption of Cyp4a10 affect synthesis of 20-HETE and EET? In a nutshell, using appropriate experiments the authors (13) could exclude 20-HETE as the culprit, in line with
previous studies showing that it is only another CYP enzyme, \textit{i.e.}, CYP4a12, which has significant 20-HETE synthase activity (14).

In contrast, EET appeared to be of interest, since it was known to be an antihypertensive molecule (15,16), the synthesis of which is sensitive to dietary salt intake (17). Inhibition of its synthesis was known to cause salt-sensitive hypertension (18).

The logical next step was to test not only whether in the knockout mice BP was salt-sensitive, but also to test whether it was responsive to amiloride. Reversal of hypertension by amiloride, which acts on the collecting duct sodium channels, would indicate that ENaC dysfunction accounts for the hypertensive phenotype of the CYP4a10\textsuperscript{-/-}—amiloride reversed hypertension on high salt; thus, the smoking gun pointed to ENaC!

Indeed, recent evidence pointed to a role of EET in the control of ENaC function. In a patch-clamp study of the rat cortical collecting duct, Wei \textit{et al.} (19) had recently shown that the precursor substance arachidonic acid decreased the activity of ENaC. This effect was specific and not mimicked by nonmetabolizable analogs of arachidonic acid. It was also not abrogated by inhibition of cyclooxygenase or of CYP450\textsubscript{o} hydroxylation, while a specific inhibitor of the CYP epoxygenase activity clearly nullified the effect of arachidonic acid on ENaC. The downstream product 11,12-EET, but not EET isomers, reduced ENaC activity. From these findings Wei \textit{et al.} concluded that the CYP-epoxygenase product 11,12-EET was the culprit.

Nakagawa \textit{et al.} (13) carried this one step further by comparing the effects of arachidonic acid and 11,12-EET on ENaC activity in the cortical collecting ducts of the CYP4a10 wild-type and knockout mice. In the CYP4a10\textsuperscript{-/-} knockout mice, basal ENaC activity was increased and, in contrast to the wild-type mice, such increased activity was virtually refractory to inhibition by arachidonic acid. In contrast to arachidonic acid in both wild-type and knockout mice, 11,12-EET was able to inhibit ENaC in the cortical collecting duct. This finding identifies lack of production of 11,12-EET by the CYP arachidonic acid monooxygenase as the crucial hypertensive pathomechanism. This hypothesis is directly supported by measurements of the metabolite 11,12-EET in the urine.

Phenomenologically the ENaC behaved as if the ENaC molecule had a gain-of-function mutation (which is the cause of the Liddle syndrome): The channel activity (open probability \times channel number) was constitutively increased in the CYP4a10\textsuperscript{-/-} mice, but was reduced when the assumed metabolic block was sidestepped by directly presenting the suspected inhibitory metabolite 11,12-EET.

A final twist was an observation implying interaction between peroxisome proliferator-activated receptor \alpha (PPAR\textalpha) and EET. Why should PPAR\textalpha be of interest in this context? It had been known that PPAR\textalpha activation can lower BP (15,20), particularly salt-dependent hypertension during chronic endothelin B receptor blockade (21), and that PPAR\textalpha causes changes in the renal expression of the CYP4A isoforms (15). A selective PPAR\textalpha agonist, Wyeth 14643, was administered to CYP4a10\textsuperscript{+/-} wild-type and CYP4a10\textsuperscript{-/-} mice to measure 11,12 epoxygenase metabolites in the urine. The long and the short of it is that Wyeth 14643 increased renal biosynthesis of EET in both CYP4a10\textsuperscript{+/-} wild-type and CYP4a10\textsuperscript{-/-} mice. It also normalized BP in hypertensive animals. This finding is of interest, since fibrates (such as PPAR\textalpha agonists) have so far been viewed only as lipid-lowering agents. Antihypertensive effects had not generated much interest and deserve further study.

Another conclusion from the findings would also be to view EET and epoxygenases as attractive candidates for potential antihypertensive interventions—if the animal data can be extrapolated to humans.

Indeed the observation of Laffer \textit{et al.} (22) pointed to a role of another arachidonic acid product, HETE, in modulating salt sensitivity by natriuretic mechanisms. Furthermore, an association was documented between hypertension and the T8590C polymorphism of the Cyp4a11 gene in the Augsburg substudy of the MONICA project (23), in line with the data from the United States by Gainer \textit{et al.} (24). It is likely that this monooxygenase plays a role in salt-sensitive hypertension of humans as well, at least in whites. Primary hypertension is certainly heterogeneous, as illustrated, to give one example, by the different behavior of
nephron numbers in hypertensive whites and in blacks, respectively: It is low in white (25,26) but not black (26) hypertensives, and in this context it is also of interest that a polymorphism in another CYP enzyme, CYP3A5, which plays a role in cortisol metabolism, has been shown to be associated with salt sensitivity and hypertension in blacks (27,28)

Finally, from a public health perspective, the expected results in this area may be of considerable relevance to provide a rationale for reduction of salt intake in the general population. Despite the clear demonstration of efficacy in the DASH (Dietary Approaches to Stop Hypertension) study (29), implementation meets considerable resistance for nonmedical reasons—to put it politely (30).

References

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