Kidney Diseases beyond Nephrology

What’s new in hypertension?

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Keywords: blood pressure; cardiovascular; death; mortality; renal insufficiency; review; stroke

Introduction

This editorial comment intends to inform readers of Nephrology Dialysis and Transplantation once a year on new information in the field of hypertension that has not been published in nephrological journals. We will review manuscripts from early 2005 to autumn 2006. Obviously, the choice of topics and manuscripts will be very subjective. Information on hypertension is published—apart from nephrology journals—in almost 10 specialty journals of hypertension and in many other areas; Medline lists 9973 citations in 2005 under the term ‘hypertension’, of which 1861 are reviews.

Human studies

Are β-blockers outdated as antihypertensive monotherapy?

Hypertension guidelines of national and international societies for decades recommended β-adrenoceptor antagonists (β-blockers) as first-line antihypertensive medication. This recommendation may change; in fact, in the very recently revised British hypertension guidelines, β-blockers are not a first choice in the drug therapy of essential hypertension. Which study triggered this revolution? After all, there is no new data apart from Lindholm et al. [1], who performed a meta-analysis of all randomized controlled trials in essential hypertension involving β-blockers as first-line agent compared with either active (13 trials, 105,951 participants) or placebo control (seven trials, 27,433 participants) and all-cause or cardiovascular mortality.

β-blockers reduce blood pressure but increase stiffness of resistance arteries

In support of the above meta-analysis [1], Savoia et al. [2] reported that sartan improves function of resistance arteries when compared with a β-blocker. The authors treated 28 people with hypertension and type-2 diabetes double-blind for 1 year with either valsartan or atenolol. Patients were pre-treated with medium doses of lisinopril and achieved identical control of blood pressure on double-blind treatment. At baseline and after 1 year, resistance arteries from gluteal
subcutaneous tissue were tested. While endothelial function was not different between groups, valsartan led to a substantial reduction of media/lumen ratio whereas atenolol did not. Atenolol treatment, but not valsartan, induced stiffer arteries. The function of resistance arteries may be critical for the maintenance of elevated blood pressure. The untoward effects of β-blockers on resistance artery function are one explanation—and there are other explanations—for their suboptimal effects on cardiovascular outcomes.

Reduction in proteinuria, a surrogate marker for the treatment of essential hypertension?

It is well established that cardiovascular events in people with hypertension are predicted by urinary albumin excretion. In other words, the greater the albuminuria, the more frequent will be such events. It was not known, however, whether treatment-induced reduction in urinary albumin excretion also predicts a better outcome in essential hypertension. Ibsen et al. [3] performed a post-hoc analysis of change of urinary albumin excretion as a predictor of cardiovascular outcomes in the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study. The latter trial enrolled over 9000 people with essential hypertension and signs of left ventricular hypertrophy. Independent of treatment, of baseline urinary albumin excretion and of changes of blood pressure, a reduction in urinary albumin excretion within the first year of treatment predicted a reduced incidence of major cardiovascular outcomes, i.e. myocardial infarction, stroke and cardiovascular death, during the 5-year follow-up. Of note, median urinary albumin excretion was low in this study, about 10 mg/g creatinine at baseline and about 6 mg/g creatinine at 1 year (depending on definition and on gender, microalbuminuria starts at about 20 mg/g creatinine).

The analysis by Ibsen et al. [3] is in agreement with a similar post-hoc analysis of the RENAAL study in people with overt nephropathy of type-2 diabetes mellitus, urinary albumin excretion >500 mg/g creatinine and hypertension, published a year earlier [4]. It is difficult to construct a direct role of urinary albumin excretion on cardiovascular outcomes. It may be that changes of urinary albumin excretion in the normal-to-microalbuminuria range merely reflect improvement of endothelial function. Changes of urinary albumin excretion in the macroalbuminuria range may be an indicator of a positive individual response to active therapy. In our view, the data strongly suggest that goals of antihypertensive therapy should include certain levels of urinary albumin excretion. The latter must be defined in future studies which prospectively include pre-specified levels of urinary albumin excretion as goals of antihypertensive therapy, in parallel with goals of blood pressure itself. Our personal consequence from the data of Ibsen et al. [3] is to monitor urinary albumin excretion in people with hypertension and reduce elevated levels of urine albumin, keeping in mind that urinary albumin excretion exhibits some intra-individual variability and that there is no ‘safe’ level of urinary albumin excretion, the lower the better, even within the normal range [5].

Does tubular proteinuria in hypertensive people predict cardiovascular risk?

To assess the cardio-renal risk in a patient, we usually measure two renal-related parameters, namely serum creatinine and urine albumin or urine protein. Little is known about other constituents of urine protein and their association with cardio-renal risk. Schrader et al. [6] followed 3500 people with uncomplicated essential hypertension and without diabetes for 3.5 years, treated all participants with ramipril and further anti-hypertensives to reach goal blood pressure. Every year, they measured 24 h ambulatory blood pressure and urine protein, -albumin and -alpha-1-microglobulin as a tubular marker. Urine markers were measured twice at baseline. Macroproteinuria, tubular proteinuria and microalbuminuria at baseline were defined by one positive result out of two. The latter unusual definition probably explains why relatively high proportions of the participants exhibited macroproteinuria (3.3%), tubular proteinuria (23%) and microalbuminuria (33%). The primary endpoint was broad (myocardial infarction, stroke, hospitalizations for heart failure or angina, revascularizations, new evidence for coronary heart disease or for peripheral vascular disease and total mortality) occurring in 331 instances. The data suggest that tubular proteinuria is as predictive for cardiovascular risk as is microalbuminuria. The concomitant presence of tubular proteinuria and of microalbuminuria is as predictive as macroproteinuria. However, the number of endpoints in each category of proteinuria in this study was low and the data need confirmation in larger trials. The authors could also confirm the data of Ibsen et al. that treatment-induced changes of urinary albumin excretion correlate with future cardiovascular risk.

Do people with hypertension have to stop drinking coffee?

Any physician caring for people with hypertension has been asked whether caffeine intake causes or contributes to high blood pressure. Winkelmayer et al. [7] presented a large-scale observational study in women that is reassuring for coffee but not for cola enthusiasts. Data from the Nurses Health Study (NHS) encompass an impressive 155,594 women followed for 12 years with 19,541 incident cases of hypertension. Habitual coffee intake was not associated with increased risk of hypertension. However, cola—be it sugared or diet variety—was associated; one can of cola per day increased the risk for hypertension in the NHS-1 and NHS-2 studies by 16% and 16%, respectively, and four or more cans by
37% and 63%, respectively (univariate; multivariate 7% and 5% as well as 16% and 19%). We will certainly never be able to randomize people for years to caffeinated and decaffeinated beverages and measure outcomes such as incidence of hypertension. Therefore, studies such as NHS will be the best available evidence to instruct our patients: they may drink coffee but should refrain from regular cola intake!

Should we start drug treatment in people with high-normal blood pressure?

Animal studies from over 10 years ago showed that treatment of young spontaneously hypertensive rats with ACE inhibitors for several weeks would reduce life-time blood pressure by more than 50 mmHg. Julius et al. [8] have now tested whether those animal experiments can be translated to humans. Mainly Caucasians with substantial overweight (mean BMI 30) and so-called high-normal blood pressure or pre-hypertension (systolic 130–139 and/or diastolic 85–89 mmHg, n = 772) were randomized to placebo or candesartan 16 mg/day for 2 years and placebo in everybody for a further 2 years. All patients received regular written advice about non-pharmacological antihypertensive therapy. In the placebo and active groups, 63% vs 53.2% developed hypertension during 4 years, an absolute difference of 9.8% which was much larger (26.8%) at 2 years when people in the active group were still on candesartan. Severe adverse cardiovascular outcomes were noted in only seven participants in 4 years. This very thorough but small trial can be considered as a valuable pilot study. The primary outcome, the incidence of hypertension, is a soft endpoint when compared to typical endpoints of major cardiovascular studies. More importantly, the effect of active treatment progressively vanished with time. The follow-up of 4 years was definitely too short to exclude the idea that there would be no further difference in hypertension incidence between active and placebo groups after, say, 6 years. Such an interval is still short, considering the life expectancy of a population with a mean age <50 years. Finally, in confirmatory studies with hard endpoints, one would need an active comparator drug in addition to a placebo control to answer the question whether blood pressure lowering or inhibition of the renin system prevents pre-hypertension from progressing to hypertension. After all, angiotensin receptor blockers are among the most expensive drugs to treat hypertension.

Haemodynamic guidance of antihypertensive therapy improves blood pressure control

Nephrologists regularly see patients referred for evaluation of so-called drug-resistant hypertension. It has been shown previously that antihypertensive therapy in such patients can be improved with knowledge of haemodynamic parameters, generated by non-invasive monitoring of cardiac output, systemic vascular resistance and intrathoracic fluid volume. Smith et al. [9] have now extended those findings to people with uncontrolled hypertension, on 1–3 antihypertensive drugs. The authors tested the hypothesis that haemodynamic monitoring by impedance cardiography would improve blood pressure control as compared to a standard ‘trial-and-error’ approach. They enrolled 164 people after a drug washout of 2 weeks, performed impedance cardiography for estimation of cardiac output, vascular resistance and intrathoracic fluid content in all participants at baseline and monthly thereafter, and randomized the participants to study investigators that did or did not know of the results of the haemodynamic parameters. After 3 months, antihypertensive therapy with haemodynamic support resulted in a significantly better control of blood pressure than expert ‘trial-and-error’ approach, normal blood pressure being achieved in 77% vs 57%. In the ‘haemodynamic’ group, vasodilators were typically advised for high peripheral vascular resistance, β-blockers for high cardiac output and diuretics for high volume states. Surprisingly, there was no difference in the number (2.0 vs 2.1), and little difference in the type of antihypertensive drugs used. If anything, inhibitors of the renin system were somewhat more and β-blockers somewhat less frequently employed in the group with haemodynamic guidance. Systemic vascular resistance was substantially lower as a result of the haemodynamic guidance, while cardiac index was identical in the two groups. On practical and economic grounds, we cannot offer haemodynamic monitoring to the vast majority of people with hypertension. However, the approach described by Smith et al. [9] may be of value in managing those with resistant hypertension despite adequate compliance.

News on antihypertensive drug adherence

It is common knowledge that patient adherence—or that of their physicians for that matter—to antihypertensive drugs could be better. Studies on antihypertensive drug adherence, however, are few and follow-up lasts usually for only 1 year and never more than 4 years. Wijk et al. [10] have now presented a 10-year follow-up in 2325 patients who started antihypertensive therapy in 1992. They linked pharmacy reports of almost 1 Mio people with hospital records and included all people with at least two prescriptions of antihypertensive drugs in 1992 and none in 1991. They excluded anybody with hospital admissions for diagnoses other than hypertension, but necessitating antihypertensive drug use, as well as all people having prescriptions of nitrates, loop diuretics, digitalis and antiarrhythmic drugs. One can calculate from other studies that such inclusion/exclusion criteria ascertain that much more than 80% of antihypertensive drugs are prescribed for hypertension. As one would expect, only about 60% remained on antihypertensive treatment after 10 years, including 40% continuous users.
and 20% re-starters. The surprising finding was that those who discontinued did so within the first year of therapy. For the treating physician, the message is to concentrate most of his/her efforts for antihypertensive drug adherence at the start of therapy, especially in people below the age of 50 years, as their adherence was definitively worse than at an older age. Also, adherence with older drugs was lower than with newer drugs: It is unknown whether the latter finding was due to side-effects, better marketing for newer drugs or other reasons.

When to screen for sleep-disordered breathing in hypertension?

Sleep-disordered breathing is associated with hypertension. This common knowledge is mainly based on studies in middle-aged people. Haas et al. [11] have reported data from the large observational ‘sleep-heart-health’ study with about 6,500 participants. The new information is that disordered sleep is strongly associated with systolic/diastolic hypertension in people younger than 60 years (odds ratio 2.38 compared with people without disordered sleep). However, there was no association of disordered sleep with systolic/diastolic hypertension in people older than 60 years and no association with isolated systolic hypertension at any age. Those data should temper our efforts to search for disordered sleep as a cause of hypertension in people >60 years and in those with isolated systolic hypertension. Sleep-disordered breathing is vastly under-diagnosed. However, the willingness of affected patients to comply with appropriated therapy (such as wearing masks while sleeping) is disappointing. It appears reasonable to restrict screening for sleep-disordered breathing to those hypertensive patients who consent to potential therapy of this breathing disorder, are younger than 60 and have systolic/diastolic hypertension.

Reversible renal damage in people with primary hyperaldosteronism

Primary hyperaldosteronism may induce renal damage [12]. New data provide some information on early stages of renal changes with primary hyperaldosteronism. Sechi et al. [13] collected longitudinal information on 50 patients with primary hyperaldosteronism followed for 5–10 years, who were compared with matched patients with essential hypertension with a mean age of about 50 years and an unknown duration of hypertension. Baseline levels of urinary albumin excretion were not different between the two groups but creatinine clearance was higher in primary hyperaldosteronism. After initiation of spironolactone therapy or adrenalectomy, there was an immediate drop in both urinary albumin excretion and creatinine clearance in primary hyperaldosteronism that was maintained throughout; those changes were substantially less in those with essential hypertension after initiation of antihypertensive therapy, although lowering of blood pressure was not different between groups. Mechanisms that may explain the changes of renal function induced by anti-aldosterone treatment were not investigated. Interestingly, serum levels of aldosterone were positively associated with urinary albumin excretion and with creatinine clearance. Nevertheless, urinary albumin excretion was not higher in those with primary hyperaldosteronism than in those with essential hypertension. The latter exhibited an unusually low percentage of individuals with normal urinary albumin excretion, namely 47%. In a further cross-sectional study, Rossi et al. [14] found higher urinary albumin excretion in primary hyperaldosteronism than in essential hypertension. These authors analyzed a population of 490 consecutive patients referred for hypertension work-up, undergoing urine collections and screening tests for hyperaldosteronism. Primary hyperaldosteronism was found in 64. The data from Sechi et al. [13] support the notion that high serum aldosterone levels can contribute to albuminuria and may be associated with hyperfiltration possibly through volume expansion. The findings corroborate other reports that aldosterone antagonism can reduce proteinuria.

Experimental studies

Extracellular matrix as a cause—and not merely a consequence—of hypertension?

It is commonly assumed that metabolism of extracellular matrix proteins in resistance blood vessels is under the influence of intravascular pressure. New evidence indicates that the reverse may also be true. In other words, extracellular matrix proteins alter blood pressure and new players enter the haemodynamic field. Zacchigna et al. [15] provide convincing evidence that Emilin1 (elastin microfibril interface-located protein 1), may profoundly determine the level of blood pressure. Emilin1 is an extracellular protein co-localized with elastic fibers and microfibrils of vessel walls, myocardium and connective tissue of other organs. Zacchigna et al. [15] wondered about the role of Emilin1 that is so abundantly expressed in the cardiovascular system. Studying the phenotype of Emilin1-null mice, they found an increase in systolic blood pressure by 19 mmHg and by 11 mmHg in heterozygous mice as compared to wild-type animals. Unexpectedly, the mechanic properties of arteries were not different between strains nor were cardiac functions. It turned out that vessel diameter was much reduced in Emilin1 null mice, causing higher peripheral arterial resistance and hypertension. Knowing the key importance of TGF-β (transforming growth factor β) for vascular development, Zacchigna et al. [15] studied in detail the intra- and extracellular generation of TGF-β. They found that Emilin1 has a pivotal role in the early stage of TGF-β maturation. Emilin1 inhibits the processing of the inactive homodimer pro-TGF-β.
In the absence of Emilin1, there is unopposed activation of TGF-β from its pro-TGF-β precursor. TGF-β has a cytostatic effect on the blood vessel wall. When the investigators reduced TGF-β gene activity in Emilin1 null mice, blood pressure came down. This study opens a new avenue in the pathophysiological understanding of hypertension. Extracellular matrix has entered the field as a pro-active, not only reactive, player.

Inhibition of the renin–angiotensin system to prevent arterial aneurysms?

TGF-β is linked to arterial wall structure in a further paper that investigated aortic aneurysm formation in a mouse model of Marfan’s syndrome. Here, the defective gene is encoding fibrillin1, another extracellular matrix protein that inhibits TGF-β. Habashi et al. [16] not only demonstrate that antibodies to TGF-β prevent aortic aneurysm formation in fibrillin1-mutant mice, but also that losartan, an angiotensin type-1 receptor blocker, completely suppresses aneurysm formation in this mouse model of Marfan’s syndrome. While these exiting data open new possibilities for treatment of aortic aneurysms, they do not answer how angiotensin type-1 receptor blockade regulates TGF-β signalling. It may be either trough-reduced activation of the angiotensin type-1 receptor or through enhanced activation of the type-2 receptor, or other mechanisms. Shortly after these challenging experimental observations, a large population-based case-control study from administrative databases in Ontario (Canada) reported that people treated with ACE inhibitors are less likely to come to the hospital with a ruptured aortic aneurysm than people not treated with those drugs [17]. Data from about 1.5 million people above the age of 64 were linked with 15,326 hospital admissions for ruptured or intact abdominal aneurysms. People receiving ACE inhibitors were less likely to present with an aneurysm (OR 0.82, 95% CI 0.74, 0.90). Similar associations were not found for other antihypertensive drugs including β-blockers, diuretics, calcium antagonists and even angiotensin receptor blockers. The database included a wide variety of risk factors, comorbid conditions, physician visits and interventions, but no information on blood pressure.

Intra- and extrarenal angiotensin type-1 receptors contribute equally to blood pressure regulation

Type-1 receptors for angiotensin II (AT1R) undoubtedly play a substantial role in the regulation of blood pressure. It is not established in which tissue(s) angiotensin II exerts its main pressor effect; it may be the kidney, the resistance vessels, the adrenal glands, the brain or other tissues, or even the concomitant activation of AT1R in several tissues. Crowley et al. [18] shed some light onto these questions by elegantly combining cross-transplantation and knock-out techniques. They generated AT1R-null mice and transplanted their kidneys into wild-type mice and vice-versa. As controls, they also transplanted wild-type kidneys into wild-type mice and AT1R-null kidneys into AT1R-null mice. Blood pressure was about 116 mmHg (mean arterial pressure, intra-arterial telemetry) in wild-type animals, 86 mmHg in AT1R-null mice and almost exactly in the middle (99 mmHg) in animals lacking either AT1R in the kidney or outside the kidney. In other words, both renal and extra-renal AT1R have a non-redundant effect on blood pressure!

Interestingly, dietary salt loading did increase blood pressure only in the absence of renal AT1R; in the presence of AT1R, a high salt diet did not alter blood pressure. Further experiments after adrenalectomy and infusions of fixed doses of aldosterone indicate that the adrenal AT1R plays no major pressure-regulatory role in this model, although mice lacking extra-renal (and thus adrenal) AT1R produce 50% less aldosterone. Data further suggest that renin release by the transplanted and denervated kidney is predominantly under baroreceptor influence. Here, the so-called short-loop feedback (angiotensin II binds to AT1R at the juxtaglomerular apparatus, this AT1R activation suppresses renin, angiotensin II formation decreases) appears to play a minor role. Thus, AT1R in the kidney, be it on vascular endothelium or on tubular epithelium, plays a unique role in blood pressure regulation which is linked to sodium handling. However, AT1R outside the kidney, and most probably outside the adrenal, have also unique and non-redundant effects independent of whether renal AT1R is present or absent. Further research will hopefully show which renal cells express AT1R relevant for blood pressure regulation and which extra-renal tissues. My favourite candidates for the latter are brain and vascular smooth muscle.

A renin receptor contributes to hypertension in a transgenic rat

Renin has long been considered as an enzyme that is secreted into the blood stream and leads there to angiotensin II formation, the latter being the active part of the system. Recent experiments show that renin has enzyme-independent effects. A renin receptor was found; binding of renin, or of pro-renin, to this receptor induces marked enhancement of renin’s enzymatic activity through conformational changes of (pro)renin as well as intracellular phosphorylation and mitogen-activated kinase activation of p42/p44, independent of angiotensin II. Burckle et al. [19] tested the role of the vascular renin receptor, by generating transgenic mice with smooth muscle-specific over-expression of the human renin receptor, by generating smooth muscle-specific transgenic rats overexpressing the human renin receptor. The transgene was effectively expressed in smooth muscle, with weak expression in heart, adrenal and kidney. Surprisingly, the animals exhibited typical biochemical features of
primary hyperaldosteronism. Plasma aldosterone doubled and aldosterone/renin ratio quadrupled. Blood pressure and heart rate increased by about 15–20%. The message is clear: renin may raise blood pressure independently of angiotensin II formation in the blood stream. In conjunction with other data showing vascular and renal damage from prorenin overexpression despite normal blood pressure, we are entering a new era of renin research. This era has some clinical bearing because specific renin inhibitors will soon be marketed as antihypertensive drugs.

**Angiotensin converting enzyme (ACE) homologue ACE2 may contribute to blood pressure regulation**

There is an interest in homologues of ACE, as previous data in mice suggested that genetic disruption of ACE2 results in heart failure. ACE2 is mainly expressed in the kidney and in the heart. Gurley et al. [20] have compared ACE2-null mice with wild-type mice of two different genetic backgrounds. The ACE2-null mice showed a normal development and no obvious anatomic or behavioural abnormality. There was no evidence of alterations in cardiac function. The major effect of the lack of ACE2 generation was a substantial reduction in the metabolism of angiotensin II, which lead to 5-fold increased levels of angiotensin II in the kidney and to an exaggerated blood pressure increase upon infusion of angiotensin II. In one of the two genetic backgrounds tested, baseline blood pressure was also slightly increased by 7 mmHg, but not in the other strain of mice. The authors propose that ACE2 may regulate angiotensin II-dependent sodium reabsorption in the kidney and thereby blood pressure. As ACE2 produces angiotensin 1-7 from angiotensin II, the former peptide may be relevant for the physiological function of ACE2. In fact, some data suggest that angiotensin 1-7 acts as a vasodilator and natriuretic agent and therefore as a blood pressure lowering peptide. Thus the renin system becomes more complicated and multi-faceted, with the need for detailed attention to experimental and clinical data.

**Acknowledgement.** I thank Prof. Karl F. Hilgers for his help in the preparation of this manuscript.

**Conflict of interest.** I have received speakers honoraria from several companies that produce antihypertensive drugs. I collaborate in several international trials on antihypertensive medications that are co-sponsored by companies that produce antihypertensive drugs.

**References**


Received for publication: 18.9.06
Accepted in revised form: 12.10.06