Kidney Diseases Beyond Nephrology

What’s new in hypertension 2007?

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Introduction

The aim of this editorial comment is to inform NDT readers of new information in the field of hypertension from mid-2006 to 2007 that has not been published in nephrological journals. No doubt the choice of topics will be very subjective; Pubmed lists 2625 citations in the last 12 months with 'hypertension' as the major topic, of which 437 are reviews. These numbers almost double if all citations are listed. In addition, the European Societies of Hypertension and of Cardiology have issued a hypertension guideline of more than 80 pages [1].

Human studies

Passive smoking in children: no effect on blood pressure but on endothelial function

Smoking and hypertension are major contributors to cardiovascular disease and to incident end-stage renal disease. Little information exists on the effects of passive smoking in young children. Kallio et al. [2] presented data from a prospective atherosclerosis prevention trial in Finland, enrolling 1054 children below the age of 1 year. At the age of 8–11 years, serum-cotinine levels were measured at the biannual visits. Flow-mediated dilatation of forearm arteries after a 4.5-min ischaemia was analysed in 402 children aged 11. In 229 children, serum cotinine was not detected; it was moderately increased in 134 and high in 39. None of the children smoked but 16% of the mothers and 25% of fathers did. There was a clear-cut reduction of flow-mediated dilatation with increasing serum-cotinine levels while blood pressure was not higher with cotinine levels. Other typical cardiovascular risk factors also showed no relationship to cotinine levels. It is well established that in adults, passive smoking reduces endothelial function. The present study establishes passive smoking as a poison for endothelial function at a very young age. The risk of passive smoking is not explained by changes of traditional risk factors, including higher blood pressure, and is not reduced by the preventive strategies that the randomized prevention trial of Kallio et al. implemented. It certainly comes as no surprise that we should protect children from passive and active smoking. The study of Kallio et al. provides a cogent argument that vascular damage from passive smoking starts very early in life; young arteries are not exempt from such damage.

Non-pharmacological interventions to lower blood pressure in people with metabolic syndrome

Given the large number of people exhibiting both hypertension and metabolic syndrome, non-pharmacological therapies are of utmost importance, not least to reduce the cost of decades of drug intake. The investigators of the PREMIER trial compared (a) advice only to (b) established life-style interventions (ELS) to (c) the latter interventions plus a DASH (dietary approaches to hypertension) diet [3]. ELS consisted of weight loss, regular exercise, low sodium and low alcohol intake, while DASH favours fruits, vegetables and low-fat dairy products. The primary outcome was blood pressure at 6 months. In the 399 people with metabolic syndrome, systolic blood pressure was reduced by 6.8 mmHg by advice, 8.4 mmHg by ELS and 9.8 mmHg by ELS + DASH. In people without metabolic syndrome (n = 397), the respective data were 6.2, 12.0 and 11.2 mmHg. The data suggest that in people with metabolic syndrome and with hypertension, a combined lifestyle and dietary approach is effective based on blood pressure alone and as effective as a typical combination of two antihypertensive drugs. The problem is the long-term adherence and outcome of non-pharmacological approaches to antihypertensive therapy.

Finally, reducing salt intake may reduce cardiovascular events

It is fairly well established that there is a link between high salt intake and high blood pressure. Also, reducing dietary salt intake reduces blood pressure in hypertensive individuals, at least in the salt-sensitive subgroups, and this...
effect of salt intake is dose dependent. Salt consumers, however, usually put forward the argument that reducing salt intake is cumbersome, difficult to adhere to and—most importantly—has never been shown to reduce cardiovascular events. Cook et al. [4] now report long-term (10–15 years) follow-up data of two randomized, controlled trials, TOHP I & II, which originally examined the effects of a low-salt diet for 18–48 months on blood pressure. Salt intake was reduced by 2–2.5 g/day, approximately a quarter of the usual intake. After 10–15 years, major cardiovascular events were reduced by a substantial degree, about 30%. This beneficial effect was independent of sex, age, body weight or blood pressure. The TOHP trials were carried out in a low-risk population. It took more than 5 years until the cumulative number of cardiovascular events diverged between randomized groups. It is not entirely clear whether this benefit of a moderate reduction in dietary salt intake was associated with an ongoing reduction in salt intake. The randomized, controlled phase of the TOHP studies had ended at that time and the now reported long-term data [4] result from an observational follow-up. In most European countries, salt intake depends mainly on processed food. To reduce salt intake, legislation to label processed food for its salt content appears mandatory, given the substantial reduction in cardiovascular risk associated with a low-salt diet. The consumer may then control his own salt intake.

Chocolate to lower blood pressure: what kind, what dose? There is an abundance of recommendations on what we should not eat or drink to lower blood pressure. Chocolate may thus be recommended. In observational studies, regular intake of cocoa is associated with reduced cardiovascular mortality. Short-term administration of cocoa (up to 2 weeks) with rather high doses of cocoa improves endothelial function and reduces blood pressure, possibly due to the action of polyphenols from cocoa. Taubert et al. [5] conducted an 18-week randomized controlled trial, investigator blinded, comparing low-dose dark (bitter) to white chocolate intake (6.3 g/day, 30 kcal) on blood pressure in 44 people with stage 1 hypertension. White chocolate does not contain polyphenols. Dark chocolate reduced blood pressure significantly by 2.9/1.9 mmHg, while white chocolate did not change it. Dark chocolate intake was associated with detectable plasma levels of polyphenols and an increase in S-nitrosoglutathione. At this low dose of dark chocolate, there were no adverse effects such as weight increase or changes in serum lipids (thus no case of addiction to chocolate). So we can recommend something pleasant to our patients with hypertension to modestly reduce blood pressure, although the evidence is still preliminary, with small sample sizes and short-term follow-up. Hopefully these data will induce others to do larger trials on cocoa and blood pressure, testing dose response and interactions with other cardiovascular risks. Perhaps the chocolate industry could provide grants.

Does acupuncture lower blood pressure? It has been shown that relaxation techniques can result in a lowering of blood pressure by several mmHg in adherent people, an effect of similar magnitude to that observed e.g. with regular exercise. Two independent studies have been published on the effects of acupuncture on blood pressure in people with stage 1–2 hypertension. The two trials used quite different designs and came to different conclusions. Flachskampf et al. [6] enrolled 160 people with uncomplicated hypertension and stable blood pressure. Drug therapy was not changed and participants were randomized to a 6-week course of either acupuncture, 30 min every other day, or sham acupuncture (single-blind). Blood pressure, the primary endpoint, was assessed by 24-h ambulatory blood pressure monitoring at baseline and at study end, and was further evaluated at 3 and 6 months. With this intensive intervention and careful assessment of endpoint as well as follow-up, the investigators came to very convincing results. Active treatment reduced blood pressure significantly by 6.4/3.7 mmHg as compared to sham acupuncture and by 5.4/3.0 mmHg as compared to baseline. However these effects during treatment were not sustained at 3- and 6-month follow-up. A further study could not quite confirm the data of Flachskampf et al. but the study design was less strict. Macklin et al. [7] randomized 190 people with hypertension to two different strategies of acupuncture or sham acupuncture. However, only up to 12 acupuncture sessions were administered during 6–8 weeks, thus much less intensively than in the Flachskampf et al. paper [6]. In addition, Macklin et al. did not continue stable antihypertensive therapy but withdrew all antihypertensives and prescribed those drugs only when blood pressure exceeded 180/100 mmHg. Blood pressure was monitored by conventional measurements every 2 weeks and no difference of blood pressure between groups was found. In the end, both studies suggest that acupuncture is not a valid option for treatment of chronic hypertension. However it may be worthwhile to examine by which mechanism(s) intensive acupuncture lowers blood pressure. Such research may find ways to control blood pressure in stressful situations in people who are susceptible to an increase in blood pressure under those conditions.

Combining angiotensin receptor blockers and ACE inhibitors: how often do adverse events occur? In many trials, adverse event reporting is surprisingly poor. Editors of major journals have recently put more emphasis on such reporting, to give more balanced information on all aspects of drug therapy. The combined administration of angiotensin receptor blockers/ACE inhibitors is effective in some cases of heart failure, of hypertension and of proteinuria [8]. Phillips et al. [9] analysed the adverse effects of such combined therapy in people with impaired left ventricular function in a quantitative review. They analysed all trials with >500 participants and adverse event reporting. They found four trials with 17 337 participants with either chronic heart failure or acute myocardial infarction with left ventricular dysfunction. In chronic heart failure, hyperkalaemia (>5.5 mM) was 4.9-fold (95% CI 2.4–9.9) more likely with the combination as with the comparator, usually an ACE inhibitor; with acute myocardial infarction, the risk for hyperkalaemia was 1.33-fold increased (95% CI 0.9–2.0). A worsening of renal function (increase of serum creatinine by >0.5 mg/dl) was also more likely with
combined therapy, 2.2 (95% CI 1.6–3.0) and 1.6 (95% CI 1.3–2.0) with chronic heart failure and with acute myocardial infarction respectively. While this study emphasizes the risk of hyperkalaemia and acute kidney injury of a common therapy in renal patients, mainly used to reduce proteinuria [8], other problems of combined therapy in heart failure, such as hypotension, are less important in renal patients who exhibit hypertension in the vast majority.

**Hypertension in pregnancy: a condition that needs follow-up**

Many textbooks consider hypertension in pregnancy a temporary condition that needs no further attention if blood pressure normalizes after giving birth. A cross-sectional, population-based study from the Netherlands challenges this view. Sabour et al. [10] invited a random sample of healthy post-menopausal women, enrolled in a nation-wide screening for breast cancer, for a CT-based coronary artery calcium score measurement (CAC score). Mean age was 67 years at the time of the CAC score. Among 491 women who were pregnant at least once, 30% reported a history of pregnancy-associated hypertension. In adjusted analysis, a history of pregnancy-associated hypertension increased the risk for a significant CAC score by about 60%. Also, pregnancy-associated hypertension increased 2.5-fold the risk for a diagnosis of hypertension in later life. Obviously, smoking and dyslipidaemia increased the risk for a significant CAC score more than a history of hypertension in pregnancy. Nevertheless, these observational data are derived from a thorough study in a representative, population-based sample and are the first to suggest hypertension in pregnancy as a coronary risk factor. As Sabour et al. [10] note, pre-eclampsia has previously been associated with metabolic syndrome and with an increased risk for cardiovascular events and death later in life. My personal conclusion is that a regular follow-up should be recommended to women with hypertension in pregnancy, independent of blood pressure after giving birth. In addition, one should monitor the children, as hypertension in pregnancy is often associated with children of low birth weight. The latter has recently been shown in a twin study to be a risk for hypertension in later life, independent of environmental and genetic factors [11]. Intervention studies are now underway to examine early cardiovascular intervention in those women.

**Resistant hypertension: time for aldosterone blockade?**

People with resistant hypertension are often appropriately referred to nephrologists. Small, uncontrolled studies suggest that spironolactone is helpful in this condition to control blood pressure. Chapman et al. [12] report results of a rather large sample of people (n = 1141) with resistant hypertension treated prospectively, uncontrolled and not randomized with spironolactone. The ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial, blood pressure lowering arm) aimed at normalizing blood pressure with a 1–3 drug regime. If blood pressure was not controlled with the mandatory three drugs, a fourth drug had to be administered and spironolactone, as well as monoxidine, were suggested choices. In the end, 1141 of the 19 257 participants received spironolactone for blood pressure management. Clinical characteristics of those 1141 people were little different from the rest of the participants, apart from a higher prevalence of diabetes mellitus; baseline serum potassium (K) was 4.2 mM. The effect of spironolactone on long-term control of blood pressure was striking, a decrease of 21.9/9.5 mmHg with very tight confidence margins. Spironolactone was started after a mean of 3.2 years in the ASCOT trial and administered for a mean of 1.3 years at 25–50 mg/day. The significant effect on blood pressure was associated with serum-K levels >5.5 mM in 4% and >6 mM in 2% and a serum creatinine >150 μM in 7% of the participants receiving spironolactone. In total, serum K increased by 0.41 mM and serum creatinine by 13 μM or 0.15 mg/dl. Breast discomfort or gynecomastia was reported in 6%, compared to 0.6% in ASCOT participants not taking spironolactone. This uncontrolled study provides valuable clinical information because of a rigorous scheme of initial antihypertensive therapy, the prospective design with frequent control of blood pressure, the stable clinical condition and stable blood pressure when spironolactone was started and the prospective documentation of adverse events. Thus we have a large database to suggest that spironolactone is a valuable fourth drug in the treatment of hypertension, at doses of 25–50 mg/day, irrespective of plasma aldosterone that was not measured in ASCOT.

**Maintain higher blood pressure, if there is intracranial artery stenosis?**

There is a strong belief in many clinicians that elevated blood pressure should not be lowered in certain situations, such as directly after a stroke or when there is stenosis of a cerebral artery. The physiological concept behind this belief is self-evident, but data in support of this are not only absent but also contradictory to this concept. All observational and interventional studies examining the association of blood pressure and stroke consistently show an inverse relationship, without a J-curve, between blood pressure and stroke risk. This relationship holds for primary prevention and also in the few intervention studies directly after a stroke. Turan et al. [13] analysed data from 567 people, all with documented intracranial artery stenosis treated in the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial. Ischaemic stroke and stroke in the same territory of the stenotic vessel were examined in relation to blood pressure during the trial. Contrary to expectations, ischaemic stroke risk increased significantly and steeply with increasing systolic and diastolic blood pressure. In the territory behind a tight stenosis, stroke risk was also higher, with higher blood pressure and with tighter stenosis. These are still observational data. However, these data and the consistent results of interventional trials argue strongly in favour of normalizing blood pressure in all people with hypertension and risk of stroke, including those with known intracranial artery stenosis.

**ADMA, a culprit further defined**

Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase and thus NO formation, accumulates in chronic kidney disease and has been associated with the devastating cardiovascular consequences of
chronic kidney disease. Kielstein et al. [14] did a straightforward experiment in healthy volunteers, to examine the effect of ADMA on cerebral perfusion and on stiffness of large arteries. ADMA was infused for 40 min during contrast-enhanced magnetic resonance imaging of the brain, and, in parallel, analysis of pulse wave velocity. ADMA reduced cerebral flow by ~15% and altered significantly the augmentation index, i.e. induced acute arterial stiffening. These changes were achieved with low-dose ADMA, leaving systemic blood pressure unchanged. This is compelling evidence that ADMA and hence NO bioavailability are involved in the regulation of arterial compliance. The question is, specifically in chronic kidney disease, how to lower ADMA levels. There is no good candidate on the horizon. In experimental settings, even after carotid surgery, administration of L-arginine was helpful.

**Vaccination against hypertension?**

Ambühl et al. [15] developed a vaccine against angiotensin II. They coupled the octapeptide via a few amino acids with a virus-like particle. Injection of this construct into rats and humans led to a consistent and effective production of anti-angiotensin II antibodies. The half-life of these antibodies is 2–3 weeks and they bind >80–90% of circulating angiotensin II. The authors also calculated that most tissue angiotensin II would be captured by the antibody. Injection of the virus-like particle plus angiotensin II construct into spontaneously hypertensive rats (SHR) reduced blood pressure by 21 mmHg, not different from a control group treated with ramipril. Phase 1 results in healthy young subjects showed a robust production of angiotensin II antibodies following the injection of 100 µg of the construct. Blood pressure was not affected at that dose in these normotensive volunteers. An abstract by the same authors reports a significant antihypertensive effect for at least 2 weeks after injection of 100–300 µg in mild–moderate hypertension, documented by 24-h blood pressure monitoring. This new development of antihypertensive therapy may be of value for people who cannot reliably take their drugs or who prefer an injection every 2–4 weeks to daily administration of drugs. I would predict, however, that there are only a very few number of patients with a stringent indication for such a new therapy. Until we can buy this antihypertensive vaccine, a lot of work has to be done to unequivocally demonstrate the safety of the vaccine. So far, no adverse events have been detected, no induction of immune complexes and associated inflammation, and the antibody production was reversible. However, only a few people have been exposed to the vaccine and Menard, in a thoughtful and detailed review [16], has exposed substantial flaws and unanswered ethical questions in the development process of this vaccine.

**Experimental studies**

**NF-kB is a pivotal switch in hypertension-induced renal and vascular injury**

In various models of hypertension-induced organ damage, including angiotensin II-induced models, nuclear factor kappa B (NF-kB) is activated. It appears that several intracellular signalling systems converge at this pivotal switch. In the resting state, NF-kB is inactive through forming a complex with its inhibitor IκB. Activators of NF-kB, e.g. angiotensin II or TNF-α, induce rapid phosphorylation of IκB, and subsequently ubiquitination and removal through the proteasome. Henke et al. [17] generated a transgenic mouse overexpressing a form of IκB lacking the phosphorylation site in endothelial cells. With this strategy, they ventured to unravel the role of endothelial NF-kB in hypertension-induced renal damage. Hypertension was induced in those mice, and in controls, by administration of a high sodium diet, infusing angiotensin II with minipumps and inhibiting NO synthase with L-NAME, all for 2 weeks when mice were sacrificed. The authors elegantly showed that NF-kB is inhibited in endothelial cells and in several substructures of the kidney in the IκB knock-in mice. IκBa, a target gene of NF-kB, is clearly less active in those mice. Interestingly, NF-kB appeared not only inhibited by IκB endothelial overexpression in the endothelium, but also in surrounding cells of the glomeruli and tubuli. Hypertension-induced albuminuria was reduced by ~50% with IκB overexpression, although blood pressure, measured by telemetry, was not reduced. Renal tubular and vascular damage was also greatly prevented with IκB overexpression, though not to levels of normotensive control mice. Glomerular damage was less reduced by IκB overexpression than the renal interstitial changes. Hypertension in this model was accompanied by significant renal expression of TNF-α, VCAM-1 and ICAM-1 that was reduced but not abrogated in the knock-in mice. Again, the beneficial effect of the knock-in model was not restricted to the endothelial cells but also to surrounding structures. Apart from reduced deposition of extracellular matrix, the kidneys of the hypertensive knock-in mice exhibited a clearly reduced infiltration of lymphocytes and macrophages. These studies underline the pivotal role of NF-kB in hypertensive renal damage and surprisingly show that reduction of NF-kB action in endothelial cells prevents vascular, interstitial and—to a lesser degree—glomerular damage. These results are encouraging, but the authors prudently point out that NF-kB inhibition may also lead to harmful effects. In LDL-receptor deficient mice, NF-kB inhibition in macrophages accelerated atherosclerosis.

**Erythropoietin can prevent vascular damage: involvement of NO synthase?**

At high doses, erythropoietin may display vascular protective effects, especially in the cerebral vasculature. Such effects occur far before any changes in haemoglobin have taken place. On the other hand, erythropoietin can induce an increase in blood pressure. Studies in mice by d'Uscio et al. [18] have shed further light on the mechanisms involved in the vascular actions of erythropoietin. The authors used wire-induced damage of carotid arteries of mice. Such damage reduces endothelium-dependent vasorelaxation to acetylcholine and promotes medial hypertrophy. Treatment with erythropoietin was initiated at 1000 U/kg body weight two times a week for 2 weeks. At the end of the 2 weeks,
erythropoietin had restored acetylcholine-dependent relaxation virtually to normal in the injured arteries and reduced medial hypertrophy to a major extent. Concomitantly, endothelial NO synthase activity increased with erythropoietin treatment. In experiments with mice deficient for the endothelial NO synthase, however, erythropoietin was not beneficial for reducing vascular injury of wire manipulation, but led to a substantial increase in blood pressure. The data suggest that erythropoietin can promote vascular repair at very high doses and that these pharmacological effects are mediated via NO formation. NO formation apparently prevents pressor effects of erythropoietin. In view of the recent findings of possible adverse cardiovascular effects of erythropoietin at higher doses in people on chronic haemodialysis or CKD, one can speculate that those adverse events are related to segments of the endothelium that are deprived of NO synthase.

A potential clue to the dilemma of antioxidants

In experimental situations of oxidant stress, antioxidants have repeatedly been shown to improve indexes of endothelial function and of related organ function. Such situations include experimental hypercholesterinaemia and hypertension. Those data and the observation in humans that a habitual high intake of antioxidants, such as vitamin E, is associated with less cardiovascular events, have led to several randomized controlled trials that however consistently showed no benefit of vitamin E on cardiovascular outcomes. Vezari et al. [19] examined the effects of combined vitamin E and C treatment for 12 weeks in normal pigs. The authors had previously demonstrated beneficial effects of antioxidants in whole animal models of endothelial damage. In normal pigs, moderate doses of vitamins E and C comparable to intervention studies in humans induced remarkable changes. The in vivo coronary dilatory response to adenosine and dobutamine was blunted by the vitamins and there was evidence of increased vascular permeability, tested by electron beam computed tomography. Moreover, coronary tissue in organ chamber from the vitamin supplement group demonstrated reduced vasodilator response to various vasodilators. Contrary to expectations, tissue content of oxidants such as superoxide and nitrotyrosine was higher in vitamin-supplemented animals. The authors speculate that antioxidants may lead to an imbalance of the endogenous redox equilibrium if the oxidant production is low. They point out that vitamin E may act as an oxidant in specific circumstances, e.g. when radical flux is low. The formation of oxidized LDL is only inhibited by vitamin E if levels of oxidants are high; if they are low, vitamin E may itself oxidize LDL, at least in the absence of vitamin C. The pig data in conjunction with the results of the large RCTs call the frequent habit of vitamin supplementation in healthy people into question.

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Conflict of interest statement. I have received speakers honoraria from several companies that produce antihypertensive drugs. I collaborate in several international trials on antihypertensive medications and on non-pharmacological treatments in CKD that are co-sponsored by companies that produce antihypertensive drugs.

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