The Global Burden of Diseases Study 2010 reported that high blood pressure is the leading risk factor for global disease burden and causes 9.4 million deaths every year—more than half of the estimated 17 million deaths a year caused by cardiovascular disease. Over 90% of patients with hypertension have essential hypertension without known cause. This syndrome rests on multiple causal factors, including genetic predisposition. Genome-wide association studies identified many genetic loci, each with small effects on blood pressure in the general population. Lifestyle and environmental factors interact with the genetic background and thereby determine the timing of hypertension onset and the magnitude of blood pressure increase. Epigenetic regulation (Figure), which alters gene expression without changing the nucleotide base sequence of genes, is emerging as one of the important regulators of transcription of specific genes involved in the pathogenesis of essential hypertension and associated risk factors, such as obesity or diabetes mellitus.

For our readers, we have collated 20 full-length articles related to the lifestyle and environmental factors that modulate the pathogenesis of hypertension. The subjects addressed range from genetically determined host characteristics (14), dietary factors (7,13), micronutrients (6), and ambient temperature (11,19), over mechanistic studies (16), to toxicity secondary to the agents produced by the intestinal microflora (3) or originating from the environment (4,5,8,9,10,12,15,18,19). Research was conducted in experimental studies (3,7,11,13,14,15,19) or in volunteers (5,8,16,18), patients (3,10,16,19), or populations (4,6,9,12,21,22). In humans, the exposure routes to pollutants encompassed the respiratory system (4,9,10,18,21,22) or the gut (5,8,9). The reviewed studies perfectly illustrate that management of the environment is an issue to be raised high on the agenda of research and health policy to prevent death and disability as a consequence of hypertension. Environmental cues that enhance the pathogenesis of hypertension preferentially affect vulnerable groups, such as pregnant women, infants and children, elderly, and patients with age-related comorbidities. This is particularly relevant for developing nations, where noncommunicable disease is exploding into an epidemic, affecting large proportions of the populations, because of nonawareness of people and leaders and too lax or not imposed environmental regulations. In line with this agenda, the Editors invite researchers worldwide to submit over the next years their best research on related topics to Hypertension.
Gut Dysbiosis Is Linked to Hypertension

Abstract
Emerging evidence suggests that gut microbiota is critical in the maintenance of physiological homeostasis. This study was designed to test the hypothesis that dysbiosis in gut microbiota is associated with hypertension because genetic, environmental, and dietary factors profoundly influence both gut microbiota and blood pressure. Bacterial DNA from fecal samples of 2 rat models of hypertension and a small cohort of patients was used for bacterial genomic analysis. We observed a significant decrease in microbial richness, diversity, and evenness in the spontaneously hypertensive rat, in addition to an increased Firmicutes/Bacteroidetes ratio. These changes were accompanied by decreases in acetate- and butyrate-producing bacteria. In addition, the microbiota of a small cohort of human hypertensive patients was found to follow a similar dysbiotic pattern because it was less rich and diverse than that of control subjects. Similar changes in gut microbiota were observed in the chronic angiotensin II infusion rat model, most notably decreased microbial richness and an increased Firmicutes/Bacteroidetes ratio. In this model, we evaluated the efficacy of oral minocycline in restoring gut microbiota. In addition to attenuating high blood pressure, minocycline was able to rebalance the dysbiotic hypertension gut microbiota by reducing the Firmicutes/Bacteroidetes ratio. These observations demonstrate that high blood pressure is associated with gut microbiota dysbiosis, both in animal and human hypertension. They suggest that dietary intervention to correct gut microbiota could be an innovative nutritional therapeutic strategy for hypertension.

Relationship Between Daily Exposure to Biomass Fuel Smoke and Blood Pressure in High-Altitude Peru

Abstract
Household air pollution from biomass fuel use affects 3 billion people worldwide; however, few studies have examined the relationship between biomass fuel use and blood pressure. We sought to determine whether daily biomass fuel use was associated with elevated blood pressure in high altitude Peru and whether this relationship was affected by lung function. We analyzed baseline information from a population-based cohort study of adults aged ≥35 years in Puno, Peru. Daily biomass fuel use was self-reported. We used multivariable regression models to examine the relationship between daily exposure to biomass fuel smoke and blood pressure outcomes. Interactions with sex and quartiles of forced vital capacity were conducted to evaluate for effect modification. Data from 1004 individuals (mean age, 55.3 years; 51.7% women) were included. We found an association between biomass fuel use with both prehypertension (adjusted relative risk ratio, 5.0; 95% confidence interval, 2.6–9.9) and hypertension (adjusted relative risk ratio, 3.5; 95% confidence interval, 1.7–7.0). Biomass fuel users had a higher systolic blood pressure (7.0 mm Hg; 95% confidence interval, 4.4–9.6) and a higher diastolic blood pressure (5.9 mm Hg; 95% confidence interval, 4.2–7.6) when compared with nonusers. We did not find interaction effects between daily biomass fuel use and sex or percent predicted forced vital capacity. We estimated using a food frequency questionnaire, was associated with a higher likelihood of having hypertension and higher blood pressure in Peru. Reducing exposure to household air pollution from biomass fuel use represents an opportunity for cardiovascular prevention.

Association Between Dietary Intake of Polychlorinated Biphenyls and the Incidence of Hypertension in a Spanish Cohort: The Seguimiento Universidad de Navarra Project

Abstract
Polychlorinated biphenyls are persistent organic pollutants that are consumed because of their bioaccumulation through the food chain. Evidence from different sources suggests a positive association between polychlorinated biphenyls exposure and the incidence of hypertension. However, no previous prospective study has investigated this potential relationship in adults. We prospectively assessed the association between dietary intake of polychlorinated biphenyls and the incidence of hypertension in a large cohort. The Seguimiento Universidad de Navarra project is a Spanish cohort of university graduates, most of them health professionals. We included 14,521 participants, initially free of hypertension, who were followed-up for a median of 8.3 years. Dietary intake of polychlorinated biphenyls was assessed at baseline through a previously validated 136-item semiquantitative food frequency questionnaire. The published concentration levels of polychlorinated biphenyls measured in samples of food consumed in Spain were used to estimate dietary intake. Multivariable Cox regression models were fitted to estimate hazard ratios and 95% confidence interval for incident hypertension. During follow-up, 1497 incident cases of medically diagnosed hypertension were identified. After adjusting for total energy intake and for potential confounders, participants in the fifth quintile of total polychlorinated biphenyls intake were at higher risk of developing hypertension (adjusted hazard ratio, 1.43 [95% confidence interval, 1.09–1.88; P for trend 0.017]) compared with those in the first quintile. In this Mediterranean cohort, dietary intake of polychlorinated biphenyls, estimated using a food frequency questionnaire, was associated with a higher risk of developing hypertension during follow-up. Nevertheless, further longitudinal studies are needed to confirm our results.
Inactive Matrix Gla Protein Is Causally Related to Adverse Health Outcomes: A Mendelian Randomization Study in a Flemish Population

Abstract
Matrix Gla protein is a vitamin K–dependent protein that strongly inhibits arterial calcification. Vitamin K deficiency leads to production of inactive nonphosphorylated and uncarboxylated matrix Gla protein (dp-ucMGP). The risk associated with dp-ucMGP in the population is unknown. In a Flemish population study, we measured circulating dp-ucMGP at baseline (1996–2011), genotyped MGP, recorded adverse health outcomes until December 31, 2012, and assessed the multivariable-adjusted associations of adverse health outcomes with dp-ucMGP. We applied a Mendelian randomization analysis using MGP genotypes as instrumental variables. Among 2318 participants, baseline dp-ucMGP averaged 3.61 μg/L. Over 14.1 years (median), 197 deaths occurred, 58 from cancer and 70 from cardiovascular disease; 85 participants experienced a coronary event. The risk of death and noncancer mortality curvilinearly increased (P<0.008) by 15.0% (95% confidence interval, 6.9–25.3) and by 21.5% (P=0.021). dp-ucMGP levels were associated (P≤0.001) with MGP variants rs2098435, rs4236, and rs2430692. For noncancer mortality and coronary events (P≤0.022), but not for total and cardiovascular mortality (P≥0.13), the Mendelian randomization analysis suggested causality. Higher dp-ucMGP predicts total, noncancer and cardiovascular mortality, but lower coronary risk. For noncancer mortality and coronary events, these associations are likely causal.

Maternal Diet During Gestation and Lactation Modifies the Severity of Salt-Induced Hypertension and Renal Injury in Dahl Salt-Sensitive Rats

Abstract
Environmental exposure of parents or early in life may affect disease development in adults. We found that hypertension and renal injury induced by a high-salt diet were substantially attenuated in Dahl SS/JrHsdMcwiCrl (SS/Crl) rats that had been maintained for many generations on the grain-based 5L2F diet compared with SS/JrHsdMcwi rats (SS/Mcw) maintained on the casein-based AIN-76A diet (mean arterial pressure, 116±9 versus 154±25 mm Hg; urinary albumin excretion, 23±12 versus 170±80 mg/d). RNAseq analysis of the renal outer medulla identified 129 and 82 genes responding to salt in SS/Mcw and SS/Crl rats, respectively, along with minor genetic differences between the SS substrains. The 129 genes responding to salt in the SS/Mcw strain included numerous genes with homologs associated with hypertension, cardiovascular disease, or renal disease in human. To narrow the critical window of exposure, we performed embryo-transfer experiments in which single-cell embryos from 1 colony (SS/Mcw or SS/Crl) were transferred to surrogate mothers from the other colony, with parents and surrogate mothers maintained on their respective original diet. All offspring were fed the AIN-76A diet after weaning. Salt-induced hypertension and renal injury were substantially exacerbated in rats developed from SS/Crl embryos transferred to SS/Mcw surrogate mothers. Conversely, salt-induced hypertension and renal injury were significantly attenuated in rats developed from SS/Mcw embryos transferred to SS/Crl surrogate mothers. Together, the data suggest that maternal diet during the gestational–lactational period has substantial effects on the development of salt-induced hypertension and renal injury in adult SS rats.

Exposure to Bisphenol A From Drinking Canned Beverages Increases Blood Pressure: Randomized Crossover Trial

Abstract
Bisphenol A (BPA) is a chemical used in plastic bottles and inner coating of beverage cans, and its exposure is almost ubiquitous. BPA has been associated with hypertension and decreased heart rate variability in the previous studies. The aim of the present study was to determine whether increased BPA exposure from consumption of canned beverage actually affects blood pressure and heart rate variability. We conducted a randomized crossover trial with noninstitutionalized adults, who were aged ≥60 years and recruited from a local community center. A total of 60 participants visited the study site 3 times, and they were provided the same beverage in 2 glass bottles, 2 cans, or 1 can and 1 glass bottle at a time. The sequence of the beverage was randomized. We then measured urinary BPA concentration, blood pressure, and heart rate variability 2 hours after the consumption of each beverage. The paired t test and mixed model were used to compare the differences. The urinary BPA concentration increased after consuming canned beverages by >1600% compared with that after consuming glass bottled beverages. Systolic blood pressure adjusted for daily variance increased by ≈4.5 mm Hg after consuming 2 canned beverages compared with that after consuming 2 glass-bottled beverages, and the difference was statistically significant. The parameters of the heart rate variability did not show statistically significant differences. The present study demonstrated that consuming canned beverage and consequent increase of BPA exposure increase blood pressure acutely.
Blood Pressure in Relation to Environmental Lead Exposure in the National Health and Nutrition Examination Survey 2003 to 2010

Abstract
In view of the declining environmental lead exposure in the United States, we analyzed the National Health and Nutrition Examination Survey (2003–2010) for association of blood pressure and hypertension with blood lead. The 12725 participants included 21.1% blacks, 20.5% Hispanics, 58.4% whites, and 48.7% women. Blacks compared with non-Blacks had higher systolic and diastolic pressures (126.5 versus 123.9 and 71.9 versus 69.6 mm Hg) and higher hypertension prevalence (44.7% versus 36.8%). Blood lead was lower in whites than in non-whites (1.46 versus 1.57 μg/dL) and in women than in men (1.25 versus 1.80 μg/dL). In multivariable analyses of all participants, blood lead doubling was associated with higher (P≤0.0007) systolic and diastolic pressure (+0.76 mm Hg; 95% confidence interval, 0.38–1.13 and +0.43 mm Hg; 0.18–0.68), but not with the odds of hypertension (0.95; 0.90–1.01; P=0.11). Associations with blood lead were nonsignificant (P≥0.09) for systolic pressure in women and for diastolic pressure in non-whites. Among men, systolic pressure increased with blood lead (P≤0.060) with effect sizes associated with blood lead doubling ranging from +0.65 mm Hg in whites to +1.61 mm Hg in blacks. For systolic pressure, interactions of ethnicity and sex with blood lead were all significant (P≤0.019). In conclusion, small and inconsistent effect sizes in the associations of blood pressure with blood lead likely exclude current environmental lead exposure as a major hypertension cause in the United States.

Ambient Air Pollution and Pregnancy-Induced Hypertensive Disorders: A Systematic Review and Meta-analysis

Abstract
Pregnancy-induced hypertensive disorders can lead to maternal and perinatal morbidity and mortality, but the cause of these conditions is not well understood. We have systematically reviewed and performed a meta-analysis of epidemiological studies investigating the association between exposure to ambient air pollution and pregnancy-induced hypertensive disorders, including gestational hypertension and preeclampsia. We searched electronic databases for English language studies reporting associations between ambient air pollution and pregnancy-induced hypertensive disorders published between December 2009 and December 2013. Combined risk estimates were calculated using random-effect models for each exposure that had been examined in ≥4 studies. Heterogeneity and publication bias were evaluated. A total of 17 articles evaluating the impact of nitrogen oxides (NOx), particulate matter (PM10, PM2.5), carbon monoxide (CO), ozone (O3), proximity to major roads, and traffic density met our inclusion criteria. Most studies reported that air pollution increased risk for pregnancy-induced hypertensive disorders. There was significant heterogeneity in meta-analysis, which included 16 studies reporting on gestational hypertension and preeclampsia as separate or combined outcomes; there was less heterogeneity in findings of the 10 studies reporting solely on preeclampsia. Meta-analyses showed increased risks of hypertensive disorders in pregnancy for all pollutants except CO. Random-effect meta-analysis-combined odds ratio associated with a 5-μg/m3 increase in PM2.5 was 1.57 (95% confidence interval, 1.26–1.96) for combined pregnancy-induced hypertensive disorders and 1.31 (95% confidence interval, 1.14–1.50) for preeclampsia [corrected]. Our results suggest that exposure to air pollution increases the risk of pregnancy-induced hypertensive disorders.

Activation of Cold-Sensing Transient Receptor Potential Melastatin Subtype 8 Antagonizes Vasoconstriction and Hypertension Through Attenuating RhoA/Rho Kinase Pathway

Abstract
Environmental cold is a nonmodifiable hypertension risk factor. Transient receptor potential melastatin subtype 8 (TRPM8) is a cold-sensing cation channel that can be activated by menthol, a compound with a naturally cold sensation in mint. Little is known about the effect of TRPM8 activation on vascular function and blood pressure. Here, we report that TRPM8 is abundantly expressed in the vasculature. TRPM8 activation by menthol attenuated vasoconstriction via RhoA/Rho kinase pathway inhibition in wild-type mice, but the effect was absent in TRPM8(−/−) mice. Chronic dietary menthol blunted mesenteric arterial constriction and lowered blood pressure in genetic hypertensive rats via inhibition of RhoA/Rho kinase expression and activity in the in vivo study. TRPM8 effect was associated with inhibition of intracellular calcium release from the sarcoplasmic reticulum, RhoA/Rho kinase activity, and sustained arterial contraction in the in vitro study. Importantly, 8-week chronic menthol capsule treatment moderately lowered systolic blood pressure and diastolic blood pressure in prehypertensive individuals compared with the placebo group. Furthermore, chronic menthol capsule administration also improved flow-mediated dilatation in prehypertensive individuals, but not in the placebo group. In conclusion, our study demonstrates that TRPM8 activation by menthol benefits vascular function and blood pressure by inhibiting calcium signaling–mediated RhoA/Rho kinase activation in the vasculature. These findings add to the evidence that long-term dietary menthol treatment had favorable effects on hypertension treatment.
Personal Black Carbon Exposure Influences Ambulatory Blood Pressure: Air Pollution and Cardiometabolic Disease (AIRCMD-China) Study

Abstract
Few prospective studies have assessed the blood pressure effect of extremely high air pollution encountered in China’s megacities. The objective of this study was to evaluate the association between combustion-related air pollution with ambulatory blood pressure and autonomic function. During February to July 2012, personal black carbon was determined for 5 consecutive days using microaethelometers in patients with metabolic syndrome in Beijing, China. Simultaneous ambient fine particulate matter concentration was obtained from the Beijing Municipal Environmental Monitoring Center and the US Embassy. Twenty-four-hour ambulatory blood pressure and heart rate variability were measured from day 4. Arterial stiffness and endothelial function were obtained at the end of day 5. For statistical analysis, we used generalized additive mixed models for repeated outcomes and generalized linear models for single/summary outcomes. Mean (SD) of personal black carbon and fine particulate matter during 24 hours was 4.66 (2.89) and 64.2 (36.9) μg/m³. Exposure to high levels of black carbon in the preceding hours was associated significantly with adverse cardiovascular responses. A unit increase in personal black carbon during the previous 10 hours was associated with an increase in systolic blood pressure of 0.53 mm Hg and diastolic blood pressure of 0.37 mm Hg (95% confidence interval, 0.17–0.89 and 0.10–0.65 mm Hg, respectively), a percentage change in low frequency to high frequency ratio of 5.11 and mean interbeat interval of −0.06 (95% confidence interval, 0.62–9.60 and −0.11 to −0.01, respectively). These findings highlight the public health effect of air pollution and the importance of reducing air pollution.

Base-Resolution Maps of 5-Methylcytosine and 5-Hydroxymethylcytosine in Dahl S Rats: Effect of Salt and Genomic Sequence

Abstract
Analysis of 5-hydroxymethylcytosine (5hmC) at single-base resolution has been largely limited to studies of stem cells or developmental stages. Given the potential importance of epigenetic events in hypertension, we have analyzed 5hmC and 5-methylcytosine (5mC) at single-base resolution in the renal outer medulla of the Dahl salt-sensitive rat and examined the effect of disease-relevant genetic or environmental alterations on 5hmC and 5mC patterns. Of CpG sites that fell within CpG islands, 11% and 1% contained significant 5mC and 5hmC, respectively. 5mC levels were substantially higher for genes with lower mRNA abundance and showed a prominent nadir around the transcription start site. In contrast, 5hmC levels were higher in genes with higher expression. Substitution of a 12.9-Mbp region of chromosome 13, which attenuates the hypertensive and renal injury phenotypes in salt-sensitive rats, or exposure to a high-salt diet, which accelerates the disease phenotypes, was associated with differential 5mC or 5hmC in several hundred CpG islands. Nearly 80% of the CpG islands that were differentially methylated in response to salt and associated with differential mRNA abundance were intragenic CpG islands. The substituted genomic segment had significant cis effects on mRNA abundance but not on DNA methylation. The study established base-resolution maps of 5mC and 5hmC in an in vivo model of disease and revealed several characteristics of 5mC and 5hmC important for understanding the role of epigenetic modifications in the regulation of organ systems function and complex diseases.

Identifying Common Genetic Variants in Blood Pressure due to Polygenic Pleiotropy With Associated Phenotypes

Abstract
Blood pressure is a critical determinant of cardiovascular morbidity and mortality. It is affected by environmental factors, but has a strong heritable component. Despite recent large genome-wide association studies, few genetic risk factors for blood pressure have been identified. Epidemiological studies suggest associations between blood pressure and several diseases and traits, which may partly arise from a shared genetic basis (genetic pleiotropy). Using genome-wide association studies summary statistics and a genetic pleiotropy-informed conditional false discovery rate method, we systematically investigated genetic overlap between systolic blood pressure (SBP) and 12 comorbid traits and diseases. We found significant enrichment of single nucleotide polymorphisms associated with SBP as a function of their association with body mass index, low-density lipoprotein, waist/hip ratio, schizophrenia, bone mineral density, type 1 diabetes mellitus, and celiac disease. In contrast, the magnitude of enrichment because of shared polygenic effects was smaller with the other phenotypes (triglycerides, high-density lipoproteins, type 2 diabetes mellitus, rheumatoid arthritis, and height). Applying the conditional false discovery rate method to the enriched phenotypes, we identified 62 loci associated with SBP (false discovery rate <0.01), including 42 novel loci. The observed polygenic overlap between SBP and several related disorders indicates that the epidemiological associations are not mediated solely via lifestyle factors but also reflect an etiologic relation that warrants further investigation. The new gene loci identified implicate novel genetic mechanisms related to lipid biology and the immune system in SBP.
Transient Neonatal High Oxygen Exposure Leads to Early Adult Cardiac Dysfunction, Remodeling, and Activation of the Renin–Angiotensin System

Abstract
Perinatal conditions (such as preterm birth) can affect adult health and disease, particularly the cardiovascular system. Transient neonatal high O2 exposure in rat in adulthood (a model of preterm birth-related complications) leads to elevated blood pressure, vascular rigidity, and dysfunction with renin–angiotensin system activation. We postulate that neonatal hyperoxic stress also affects myocardial structure, function, and expression of renin–angiotensin system components. Sprague–Dawley pups were kept with their mother in 80% O2 or in room air (control) from days 3 to 10 of life. Left ventricular function was assessed in 4-, 7-, 12-week-old (echocardiography) and in 16-week-old (intraventricular catheterization) male O2-exposed versus control rats. At 16 weeks, hearts from O2-exposed rats showed cardiomyocyte hypertrophy, enhanced fibrosis, and increased expression of transforming growth factor-beta1, senescence-associated proteins p53 and Rb, upregulation of angiotensin II type 1 (AT1) receptor expression (protein and AT1a/b mRNA), and downregulation of AT2 receptors. At 4 weeks (before blood pressure increase), the expression of cardiomyocyte surface area, fibrosis, p53, and AT1b was significantly increased and AT2 decreased in O2-exposed animals. After 4 weeks of continuous angiotensin II infusion (starting at 12 weeks), O2-exposed rats developed severe heart failure, with impaired myocardial mechanical properties compared with saline-infused rats. Transient neonatal O2 exposure in rats leads to left ventricular hypertrophy, fibrosis, and dysfunction and increased susceptibility to heart failure under pressure overload. These results are relevant to the growing population of individuals born preterm who may be at higher risk of cardiac dysfunction when faced with increased peripheral resistance associated with hypertension, vascular diseases, and aging.

Resistance Artery Creatine Kinase mRNA and Blood Pressure in Humans

Abstract
Hypertension remains the main risk factor for cardiovascular death. Environmental and biological factors are known to contribute to the condition, and circulating creatine kinase was reported to be the main predictor of blood pressure in the general population. This was proposed to be because of high resistance artery creatine kinase rapidly regenerating ATP for vascular contractility. Therefore, we assessed whether creatine kinase isoenzyme mRNA levels in human resistance arteries are associated with blood pressure. We isolated resistance-sized arteries from omental fat donated by consecutive women undergoing uterine fibroid surgery. Blood pressure was measured in the sitting position. Vessels of 13 women were included, 6 normotensive and 7 hypertensive, mean age 42.9 years (SE, 1.6), and mean systolic/diastolic blood pressure, 144.8 (8.0)/86.5 (4.3) mm Hg. Arteriolar creatine kinase isoenzyme mRNA was assessed using quantitative real-time polymerase chain reaction. Normalized creatine kinase B mRNA copy numbers, ranging from 5.2 to 24.4 (mean, 15.0; SE, 1.9), showed a near-perfect correlation with diastolic blood pressure (correlation coefficient, 0.9; 95% confidence interval, 0.6–1.0) and were well correlated with systolic blood pressure, with a 90% relative increase in resistance artery creatine kinase B mRNA in hypertensives compared with normotensives, and normalized copy numbers were, respectively, 19.3 (SE, 2.0) versus 10.1 (SE, 2.1), P=0.0045. To our knowledge, this is the first direct evidence suggesting that resistance artery creatine kinase mRNA expression levels concur with blood pressure levels, almost doubling with hypertension. These findings add to the evidence that creatine kinase might be involved in the vasculature’s pressor responses.

Metabolomics and Incident Hypertension Among Blacks: The Atherosclerosis Risk in Communities Study

Abstract
Development of hypertension is influenced by genes, environmental effects, and their interactions, and the human metabolome is a measurable manifestation of gene–environment interaction. We explored the metabolomic antecedents of developing incident hypertension in a sample of blacks, a population with a high prevalence of hypertension and its comorbidities. We examined 896 black normotensives (565 women; aged, 45–64 years) from the Atherosclerosis Risk in Communities study, whose metabolome was measured in serum collected at the baseline examination and analyzed by high-throughput methods. The analyses presented here focus on 204 stably measured metabolites during a period of 4 to 6 weeks. Weibull parametric models considering interval censored data were used to assess the hazard ratio for incident hypertension. We used a modified Bonferroni correction accounting for the correlations among metabolites to define a threshold for statistical significance (P<3.9×10−4). During 10 years of follow-up, 38% of baseline normotensives developed hypertension (n=344). With adjustment for traditional risk factors and estimated glomerular filtration rate, each +1SD difference in baseline 4-hydroxy hippurate, a product of gut microbial fermentation, was associated with 17% higher risk of hypertension (P=2.5×10−4), which remained significant after adjusting for both baseline systolic and diastolic blood pressure (P=3.8×10−4). After principal component analyses, a sex steroids pattern was significantly associated with risk of incident hypertension (highest versus lowest quintile hazard ratio, 1.72; 95% confidence interval, 1.05–2.82; P for trend, 0.03), and stratified analyses suggested that this association was consistent in both sexes. Metabolomic analyses identify novel pathways in the pathogenesis of hypertension.
Acute Exposure to Diesel Exhaust Impairs Nitric Oxide–Mediated Endothelial Vasomotor Function by Increasing Endothelial Oxidative Stress

Abstract
Exposure to diesel exhaust was recently identified as an important cardiovascular risk factor, but whether it impairs nitric oxide (NO)–mediated endothelial function and increases production of reactive oxygen species (ROS) in endothelial cells is not known. We tested these hypotheses in a randomized, controlled, crossover study in healthy male volunteers exposed to ambient and polluted air (n=12). The effects of skin microvascular hyperemic provocative tests, including local heating and iontophoresis of acetylcholine and sodium nitroprusside, were assessed using a laser Doppler imager. Before local heating, skin was pretreated using a laser Doppler imager. Before sodium nitroprusside, were assessed iontophoresis of acetylcholine and tests, including local heating and air (n=12). The effects of skin exposed to ambient and polluted study in healthy male volunteers known. We tested these hypotheses in a randomized, controlled, crossover of reactive oxygen species (ROS) in endothelial cells is not known. We tested these hypotheses in a randomized, controlled, crossover study in healthy male volunteers exposed to ambient and polluted air (n=12). The effects of skin microvascular hyperemic provocative tests, including local heating and iontophoresis of acetylcholine and sodium nitroprusside, were assessed using a laser Doppler imager. Before local heating, skin was pretreated using a laser Doppler imager. Before sodium nitroprusside, were assessed iontophoresis of acetylcholine and tests, including local heating and air (n=12). The effects of skin exposed to ambient and polluted study in healthy male volunteers.

Postnatal Sulfur Dioxide Exposure Reversibly Alters Parasympathetic Regulation of Heart Rate

Abstract
Perinatal sulfur dioxide exposure disrupts parasympathetic regulation of cardiovascular activity. Here, we examine the relative risks of prenatal versus postnatal exposure to the air pollutant and the reversibility of the cardiovascular effects. Two groups of animals were used for this study. For prenatal exposure, pregnant Sprague–Dawley dams were exposed to 5 parts per million sulfur dioxide for 1 hour daily throughout gestation and with their pups after birth to medical-grade air through 6 days postnatal. For postnatal exposure, dams were exposed to air and after delivery along with their pups to 5 parts per million sulfur dioxide through postnatal day 6. ECGs were recorded from pups on postnatal day 5 to examine changes in heart rate. Whole-cell patch-clamp electrophysiology was used to examine changes in neurotransmission to cardiac vagal neurons in the nucleus ambiguus on sulfur dioxide exposure. Postnatal sulfur dioxide exposure diminished glutamatergic neurotransmission to cardiac vagal neurons by 40.9% and increased heart rate, whereas prenatal exposure altered neither of these properties. When postnatal exposure concluded on postnatal day 5, excitatory neurotransmission remained decreased through day 6 and returned to basal levels by day 7. ECGs showed that heart rate remained elevated through day 6 and recovered by day 7. On activation of the parasympathetic diving reflex, the response was significantly blunted by postnatal sulfur dioxide exposure through day 7 but recovered by day 8. Postnatal, but not prenatal, exposure to sulfur dioxide can disrupt parasympathetic regulation of cardiovascular activity. Neonates can recover from these effects within 2 to 3 days of discontinued exposure.

Seasonal Blood Pressure Changes: An Independent Relationship With Temperature and Daylight Hours

Abstract
Seasonal blood pressure (BP) changes have been found to be related to either outdoor or indoor temperature. No information regarding the independent effects of temperature measured proximally to the patient, the personal-level environmental temperature (PET), is available. Inclusion of daylight hours in multivariate analysis might allow exploring the independent interaction of BP with seasonality. To investigate whether ambulatory BP monitoring is affected by PET or by seasonality, 1897 patients referred to our hypertension units underwent ambulatory BP monitoring with a battery-powered temperature data logger fitted to the carrying pouch of the monitor. Predictors of 24-hour daytime and nighttime BP and of morning BP surge were investigated with a multivariate stepwise regression model, including age, sex, body mass index, antihypertensive treatment, office BP, ambulatory heart rate, PET, relative humidity, atmospheric pressure, and daylight hours as independent variables. At adjusted regression analysis, daytime systolic BP was negatively related to PET (−0.14; 95% confidence interval, −0.25 to −0.02); nighttime BP was positively related to daytime hours (0.63; 0.37–0.90); and morning BP surge was negatively related to daytime hours (−0.54; −0.87 to −0.21). These results provide new evidence that PET and seasonality (daylight hours) are 2 independent predictors of ambulatory BP monitoring.
Association Between Long-Term Air Pollution and Increased Blood Pressure and Hypertension in China

Abstract
Several studies have investigated the short-term effects of ambient air pollutants in the development of high blood pressure and hypertension. However, little information exists regarding the health effects of long-term exposure. To investigate the association between residential long-term exposure to air pollution and blood pressure and hypertension, we studied 24,845 Chinese adults in 11 districts of 3 northeastern cities from 2009 to 2010. Three-year average concentration of particles with an aerodynamic diameter ≤10 μm (PM₁₀), sulfur dioxide (SO₂), nitrogen oxides (NOₓ), and ozone (O₃) were calculated from monitoring stations in the 11 districts. We used generalized additive models and 2-level logistic regression models to examine the health effects. The results showed that the odds ratio for hypertension increased by 1.12 (95% confidence interval [CI], 1.08–1.16) per 19 μg/m³ increase in PM₁₀, 1.11 (95% CI, 1.04–1.18) per 20 μg/m³ increase in SO₂, and 1.13 (95% CI, 1.06–1.20) per 22 μg/m³ increase in O₃. The estimated increases in mean systolic and diastolic blood pressure were 0.87 mmHg (95% CI, 0.48–1.27) and 0.32 mmHg (95% CI, 0.08–0.56) per 19 μg/m³ interquartile increase in PM₁₀, 0.80 mmHg (95% CI, 0.46–1.14) and 0.31 mmHg (95% CI, 0.10–0.51) per 20 μg/m³ interquartile increase in SO₂, and 0.73 mmHg (95% CI, 0.35–1.11) and 0.37 mmHg (95% CI, 0.14–0.61) per 22 μg/m³ interquartile increase in O₃. These associations were only statistically significant in men. In conclusion, long-term exposure to PM₁₀, SO₂, and O₃ was associated with increased arterial blood pressure and hypertension in the study population.

Association of Serum Cotinine Levels and Hypertension in Never Smokers

Abstract
Hypertension is a major public health problem. Identifying novel risk factors for hypertension, including widely prevalent environmental exposures, is therefore important. Active smoking is a well-known risk factor for hypertension and cardiovascular diseases. However, there are no studies investigating the relationship between secondhand smoke exposure, measured objectively by serum cotinine, and high blood pressure among never smokers. We examined 2,889 never smokers from the National Health and Nutrition Examination Survey 2005 to 2008. Our exposure of interest was secondhand smoke exposure among never smokers, estimated by serum cotinine level, and our main outcome was hypertension (n=1004). We found that in never smokers, higher serum cotinine levels were positively associated with hypertension. In comparison with those with serum cotinine levels ≤0.218 ng/mL, the multivariable odds ratio (95% CI, 0.86–5.63) per 0.218 ng/mL increased in serum cotinine levels was 1.44 (1.01–2.04). Additionally, serum cotinine was positively associated with mean change in systolic blood pressure (odds ratio [95% confidence interval], 3.24 [0.86–5.63]; P=0.0061). However, no association was present with diastolic blood pressure. In conclusion, in never smokers, higher secondhand smoke exposure measured objectively by serum cotinine levels was found to be associated with systolic blood pressure and hypertension independent of age, sex, ethnicity, education, alcohol drinking, body mass index, glycohemoglobin, total cholesterol, and other confounders.

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