EDITORS’ PICKS

Hypertension Editors’ Picks

Gut Microbiome

The Editors

The following articles are highlighted as part of Hypertension’s Editors’ Picks series. Combined with computational methods, advances in sequencing technologies in the last decade have allowed us to characterize the gut microbiome, the genome of the collection of microorganisms that inhabit the gastrointestinal tract. Following a seminal article published in Hypertension by Yang and colleagues in 2015, the gut microbiota has emerged as an important contributor to blood pressure (BP) regulation. By using fecal microbiota transplants, germfree animals, and antibiotic treatments, the field has been consistently moving from association to causation in both experimental and clinical settings. Among the many factors that influence the composition of the gut microbiota, a major driver is diet, which is also important for BP regulation. Well-established dietary factors that control BP, such as sodium and fiber intake, are now known to impact BP via the gut microbiota. Together with reviews and guidelines for gut microbiome studies in experimental and clinical hypertension, the articles in this collection represent important advances in the hypertension field. They include, for example, the first study to characterize the gut microbiota of men whose BP was measured by ambulatory BP monitoring. New machine learning strategies were able to identify participants with cardiovascular disease based on their gut microbiome, and the transition from cardiac hypertrophy to heart failure in rats. However, our understanding of the roles of the gut microbiota in hypertension is still in its infancy. The biggest challenge for future studies is to provide evidence that the microbiome has a causal function for the regulation of BP and cardiovascular disease by shifting focus from taxonomic (“Who’s there?”) to functional (“What are they doing?”) analyses. We also need to elucidate the function of known and new microbiota-derived metabolites including their interaction with the host immune system and cardiovascular target organs. Altogether, a better understand of the microbiome-host interaction may lead to new treatment targets for cardiovascular disease.

Gut Microbiota and Host Plasma Metabolites in Association With Blood Pressure in Chinese Adults

Abstract

Animal studies have revealed gut microbial and metabolic pathways of blood pressure (BP) regulation, yet few epidemiological studies have collected microbiota and metabolomics data in the same individuals. In a population-based, Chinese cohort who did not report antihypertension medication use (30–69 years, 54% women), thus minimizing BP treatment effects, we examined multivariable-adjusted (eg, diet, physical activity, smoking, kidney function), cross-sectional associations between measures of gut microbiota (16S rRNA [ribosomal RNA], N=1003), and plasma metabolome (liquid chromatography-mass spectrometry, N=434) with systolic blood pressure (SBP, mean [SD]=126.0 [17.4] mm Hg) and diastolic blood pressure (DBP [80.7 (10.7) mm Hg]). We found that the overall microbial community assessed by principal coordinate analysis varied by SBP and DBP (permutational multivariate ANOVA, P<0.05). To account for strong correlations across metabolites, we first examined metabolite patterns derived from principal component analysis and found that a lipid pattern was positively associated with SBP (linear regression coefficient [95% CI] per 1 SD pattern score: 2.23 [0.72–3.74] mm Hg) and DBP (1.72 [0.81–2.63] mm Hg). Among 1104 individual metabolites, 34 and 39 metabolites were positively associated with SBP and DBP (false discovery rate–adjusted linear model P<0.05), respectively, including linoleate, palmitate, dihomolinolenate, 8 sphingomyelins, 4 acyl-carnitines, and 2 phosphatidylinositols. Subsequent pathway analysis showed that metabolic pathways of long-chain saturated acylcarnitine, phosphatidylinositol, and sphingomyelins were associated with SBP and DBP (false discovery rate–adjusted Fisher exact test P<0.05). Our results suggest potential roles of microbiota and metabolites in BP regulation to be followed up in prospective and clinical studies.
**Editors’ Picks**

**Butyrate Regulates COVID-19-Relevant Genes in Gut Epithelial Organoids From Normotensive Rats**

**Abstract**
It is increasingly evident that patients with hypertension are at high risk for coronavirus disease 2019 (COVID-19) and exhibit gastrointestinal symptoms suggesting that impaired gut-lung communications could be responsible, at least in part, for the multiorgan pathologies including cardiovascular manifestations of this disease.1 Higher expression of ACE2 (angiotensin-converting enzyme-2) and TMPRSS2 (transmembrane protease serine-2), key molecules in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, in gut epithelium from spontaneously hypertensive rats supports this view.2 Finally, changes in gut microbiome associated with short-chain fatty acids, particularly butyrate, is found in both hypertension and COVID-19.1 Butyrate is an HDAC (histone deacetylase) inhibitor that maintains acetylation of histones, affecting chromatin organization and gene expression. Therefore, we sought to test the hypothesis that increased risk of COVID-19 in hypertension could, in part, be due to cumulative depletion of butyrate-producing gut bacteria leading to decreases in butyrate.1 Therefore, treatment with this short-chain fatty acid would regulate ACE2 and its partners influencing antiviral genes. This could be critical in the control of gut viral infection and rebalancing of the gut-lung axis.

**Microbiota Introduced to Germ-Free Rats Restores Vascular Contractility and Blood Pressure**

**Abstract**
Commensal gut microbiota are strongly correlated with host hemodynamic homeostasis but only broadly associated with cardiovascular health. This includes a general correspondence of quantitative and qualitative shifts in intestinal microbial communities found in hypertensive rat models and human patients. However, the mechanisms by which gut microbes contribute to the function of organs important for blood pressure (BP) control remain unanswered. To examine the direct effects of microbiota on BP, we conventionalized germ-free (GF) rats with specific pathogen-free rats for a short-term period of 10 days, which served as a model system to observe the dynamic responses when reconstituting the holobiome. The absence of microbiota in GF rats resulted with relative hypotension compared with their conventionalized counterparts, suggesting an obligatory role of microbiota in BP homeostasis. Hypotension observed in GF rats was accompanied by a marked reduction in vascular contractility. Both BP and vascular contractility were restored by the introduction of microbiota to GF rats, indicating that microbiota could impact BP through a vascular-dependent mechanism. This is further supported by the decrease in actin polymerization in arteries from GF rats. Improved vascular contractility in conventionalized GF rats, as indicated through stabilized actin filaments, was associated with an increase in cofilin phosphorylation. These data indicate that the vascular system senses the presence (or lack of) microbiota to maintain vascular tone via actin polymerization. Overall, these results constitute a fundamental discovery of the essential nature of microbiota in BP regulation.

**SARS-CoV-2 Receptor ACE2 (Angiotensin-Converting Enzyme 2) Is Upregulated in Colonic Organoids From Hypertensive Rats**

**Abstract**
Hypertension is the most common comorbidity associated with unfavorable outcomes in patients with coronavirus disease 2019 (COVID-19). This especially impacts the elderly population with its underlying high rate of hypertension.1 Emerging evidence also implicates the gastrointestinal tract in COVID-19, with ≈30% to 50% of patients presenting with gastrointestinal symptoms. Nasal, pulmonary, and gastrointestinal epithelia express high levels of ACE2 (angiotensin-converting enzyme 2), the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry.2 While the primary mode of viral transmission is inhalation of respiratory droplets, the gastrointestinal epithelium is the body site with greatest ACE2 expression.2 Moreover, a critical role for gut in COVID-19 pathophysiology is emerging that is potentially relevant for hypertension-COVID-19 comorbidity: (1) ≈30% to 50% COVID-19 of patients manifest gastrointestinal symptoms, often before respiratory symptoms1; (2) infectious severe acute respiratory syndrome coronavirus 2 has been detected in stool, with viral RNA shedding in feces for weeks;3 (3) all patients with COVID-19 show altered fecal microbiome and dysbiosis, even those without gastrointestinal symptoms;4 and some of those bacterial species adversely influence ACE2; (4) gut mucosa exhibits all components of renin-angiotensin system; and (5) the intestinal epithelium supports severe acute respiratory syndrome coronavirus 2 replication.2 These observations led us to hypothesize that increased ACE2 expression in gut epithelium would predispose hypertension patients to COVID-19 infection. We tested this hypothesis in organoid cultures from spontaneously hypertensive rats (SHR) using Wister Kyoto rats (WKY) as controls.
Machine Learning Strategy for Gut Microbiome–Based Diagnostic Screening of Cardiovascular Disease

Abstract
Cardiovascular disease (CVD) is the number one leading cause for human mortality. Besides genetics and environmental factors, in recent years, gut microbiota has emerged as a new factor influencing CVD. Although cause-effect relationships are not clearly established, the reported associations between alterations in gut microbiota and CVD are prominent. Therefore, we hypothesized that machine learning (ML) could be used for gut microbiome-based diagnostic screening of CVD. To test our hypothesis, fecal 16S ribosomal RNA sequencing data of 478 CVD and 473 non-CVD human subjects collected through the American Gut Project were analyzed using 5 supervised ML algorithms including random forest, support vector machine, decision tree, elastic net, and neural networks. Thirty-nine different differential bacterial taxa were identified between the CVD and non-CVD groups. ML modeling using these taxonomic features achieved a testing area under the receiver operating characteristic curve of 0.70. Overall, our study is the first to demonstrate a gut microbiome-based diagnostic strategy for preventing HF.

Gut Microbiota Profile Identifies Transition From Compensated Cardiac Hypertrophy to Heart Failure in Hypertensive Rats

Abstract
Microcirculatory alterations displayed by patients with heart failure (HF) induce structural and functional intestinal changes that may affect normal gut microbial community. At the same time, gut microbiota can influence pathological mechanisms implicated in HF progression. However, it is unknown whether gut microbiota dysbiosis can precede the development of cardiac alterations in HF or if it is only a mere consequence. Our aim was to investigate the potential relationship between gut microbiota composition and HF development by comparing spontaneously hypertensive heart failure and spontaneously hypertensive rat models. Gut microbiota from spontaneously hypertensive heart failure, spontaneously hypertensive rat, and normotensive Wistar Kyoto rats at 9 and 19 months of age was analyzed by sequencing the 16S ribosomal RNA gene, and KEGG metabolic pathways associated to 16S profiles were predicted. Beta diversity, Firmicutes/Bacteroidetes ratio, taxonomic abundances, and potential metabolic functions of gut microbiota were significantly different in spontaneously hypertensive heart failure with respect to spontaneously hypertensive rats before (9 months) and after (19 months) cardiac differences were presented. Nine-month-old spontaneously hypertensive heart failure showed a significant increase in the genera Paraprevotella, Oscillibacter, Prevotella 9, Faecalitalea, Faecalibacterium, Ruminoclostridium 6, Phascolarctobacterium, Butyrivibrio, Parabacteroides, and Para-bacteroides compared with both Wistar Kyoto and spontaneously hypertensive rats, while Ruminoclostridium 9, Oscillibacter, Ruminoclostridium, Mucispirillum, Intestinimonas, and Akkermansia were diminished. Of them, Akkermansia, Prevotella 9, Paraprevotella, and Phascolarctobacterium were associated to changes in cardiac structure and function. Our results demonstrate an association between specific changes in gut microbiota and the development of HF in a hypertensive model of HF and further support the intervention to restore gut microbiota as an innovative therapeutic strategy for preventing HF.
Altered Gut Microbiome Profile in Patients With Pulmonary Arterial Hypertension

Abstract
Pulmonary arterial hypertension (PAH) is considered a disease of the pulmonary vasculature. Limited progress has been made in preventing or arresting progression of PAH despite extensive efforts. Our previous studies indicated that PAH could be considered a systemic disease since its pathology involves interplay of multiple organs. This, coupled with increasing implication of the gut and its microbiome in chronic diseases, led us to hypothesize that patients with PAH exhibit a distinct gut microbiome that contributes to, and predicts, the disease. Fecal microbiome of 18 type 1 PAH patients (mean pulmonary arterial pressure, 57.4; SD, 16.7 mm Hg) and 13 reference subjects were compared by shotgun metagenomics to evaluate this hypothesis. Significant taxonomic and functional changes in microbial communities in the PAH cohort were observed. Pathways for the synthesis of arginine, proline, and ornithine were increased in PAH cohort compared with reference cohort. Additionally, groups of bacterial communities associated with trimethylamine/trimethylamine N-oxide and purine metabolism were increased in PAH cohort. In contrast, butyrate- and propionate-producing bacteria such as Coprococcus, Butyrivibrio, Lachnospiraceae, Eubacterium, Akkermansia, and Bacteroides were increased in reference cohort. A random forest model predicted PAH from the composition of the gut microbiome with 83% accuracy. Finally, virome analysis showed enrichment of Enterococcal and relative depletion of Lactococcal phages in the PAH cohort. In conclusion, patients with PAH exhibit a unique microbiome profile that has the high predictive potential for PAH. This highlights previously unknown roles of gut bacteria in this disease and could lead to new therapeutic, diagnostic, or management paradigms for PAH.

Maternal Treatment With Captopril Persistently Alters Gut-Brain Communication and Attenuates Hypertension of Male Offspring

Abstract
Maternal-fetal crosstalk has been implicated in long-term control of the health of offspring, including transgenerational hypertension. However, current knowledge is limited about maternal influences on the gut and its microbiome in blood pressure control in offspring. Therefore, the current study was designed to test the hypothesis that maternal factors influence the gut-brain axis impacting hypertension in offspring. We elected to use captopril, an antihypertensive angiotensin-converting enzyme inhibitor that possesses antibacterial properties, for the study. Pregnant female spontaneously hypertensive rats and normotensive Wistar Kyoto rats were treated with captopril water (100 mg/[kg.day]) or sterile water throughout pregnancy and lactation. At weaning, the pups from dams drinking sterile water were continued with sterile water until 12 weeks of age. The male pups from dams drinking captopril water were divided at weaning into 2 groups: offspring drinking captopril water and offspring withdrawn from captopril water, then drinking sterile water until 12 weeks of age. Captopril changed gut microbiota of spontaneously hypertensive rat dams, and some of these changes were reflected in their 12-week-old male offspring. These 12-week-old spontaneously hypertensive rat male offspring exposed to captopril via dams demonstrated persistently decreased systolic blood pressure, decreased number of activated microglia and neuroinflammation, as well as improvement of gut inflammation and permeability. Therefore, maternal captopril treatment improves the dysregulated gut-brain axis in spontaneously hypertensive rat male offspring, providing conceptual support that targeting the gut-brain axis via the mother may be a viable strategy for control of hypertension in the offspring.

Microbial Peer Pressure: The Role of the Gut Microbiota in Hypertension and Its Complications

Abstract
There is increasing evidence of the influence of the gut microbiota on hypertension and its complications, such as chronic kidney disease, stroke, heart failure, and myocardial infarction. This is not surprising considering that the most common risk factors for hypertension, such as age, sex, medication, and diet, can also impact the gut microbiota. For example, sodium and fermentable fiber have been studied in relation to both hypertension and the gut microbiota. By combining second- and, now, third-generation sequencing with metabolomics approaches, metabolites, such as short-chain fatty acids and trimethylamine N-oxide, and their producers, have been identified and are now known to affect host physiology and the cardiovascular system. The receptors that bind these metabolites have also been explored with positive findings—examples include known short-chain fatty acid receptors, such as G-protein coupled receptors GPR41, GPR43, GPR109a, and OLF78 in mice. GPR41 and OLF78 have been shown to have inverse roles in blood pressure regulation, whereas GPR43 and GPR109A have to date been demonstrated to impact cardiac function. New treatment options in the form of prebiotics (eg, dietary fiber), probiotics (eg, Lactobacillus spp.), and postbiotics (eg, the short-chain fatty acids acetate, propionate, and butyrate) have all been demonstrated to be beneficial in lowering blood pressure in animal models, but the underlying mechanisms remain poorly understood. Here, we review the evidence for the role of the gut microbiota in hypertension, its risk factors, and cardiorenal complications and identify future directions for this exciting and fast-evolving field.
Editors’ Picks

Gut Pathology and Its Rescue by ACE2 (Angiotensin-Converting Enzyme 2) in Hypoxia-Induced Pulmonary Hypertension

Abstract
Therapeutic advances for pulmonary hypertension (PH) have been incremental because of the focus on the pulmonary vasculature in PH pathology. Here, we evaluate the concept that PH is, rather, a systemic disorder involving interplay among multiorgan systems, including brain, gut, and lungs. Therefore, the objective of this study was to evaluate the hypothesis that PH is associated with a dysfunctional brain-gut-lung axis and that global overexpression of ACE2 (angiotensin-converting enzyme 2) rebalances this axis and protects against PH. ACE2 knockin and wild-type (WT; C57BL/6) mice were subjected to chronic hypoxia (10% FIO2) or room air for 4 weeks. Cardiopulmonary hemodynamics, histology, immunohistochemistry, and fecal 16S rRNA microbial gene analyses were evaluated. Hypoxia significantly increased right ventricular systolic pressure, sympathetic activity, as well as the number and activation of microglia in the paraventricular nucleus of the hypothalamus in WT mice. This was associated with a significant increase in muscularis layer thickening and decreases in both villi length and goblet cell numbers. ACE2 (Angiotensin-Converting Enzyme 2) rebalances these hypoxia-induced pathologies and attenuates PH. The data implicate dysfunctional brain-gut-lung communication in PH and provide novel avenues for therapeutic interventions.

Guidelines for Transparency on Gut Microbiome Studies in Essential and Experimental Hypertension

Abstract
Hypertension is a complex and modifiable condition in which environmental factors contribute to both onset and progression. Recent evidence has accumulated for roles of diet and the gut microbiome as environmental factors in blood pressure regulation. However, this is complex because gut microbiomes are a unique feature of each individual reflecting that individual’s developmental and environmental history creating caveats for both experimental models and human studies. Here, we describe guidelines for conducting gut microbiome studies in experimental and clinical hypertension. We provide a complete guide for authors on proper design, analyses, and reporting of gut microbiota/microbiome and metabolite studies and checklists that can be used by reviewers and editors to support robust reporting and interpretation. We discuss factors that modulate the gut microbiota in animal (eg, cohort, controls, diet, developmental age, housing, sex, and models used) and human studies (eg, blood pressure measurement and medication, body mass index, demographic characteristics including age, cultural identification, living structure, sex and socioeconomic environment, and exclusion criteria). We also provide best practice advice on sampling, storage of fecal/cecal samples, DNA extraction, sequencing methods (including metagenomics and 16S rRNA), and computational analyses. Finally, we discuss the measurement of short-chain fatty acids, metabolites produced by the gut microbiota, and interpretation of data. These guidelines should support better transparency, reproducibility, and translation of findings in the field of gut microbiota/microbiome in hypertension and cardiovascular disease.

Gut Microbiota and Fecal Levels of Short-Chain Fatty Acids Differ Upon 24-Hour Blood Pressure Levels in Men

Abstract
Gut microbiota may influence blood pressure (BP), namely via end products of carbohydrate fermentation. After informed consent, male volunteers were prospectively categorized into 3 groups upon European Society of Hypertension criteria based on 24-hour ambulatory BP measurements: (1) hypertension, (2) borderline hypertension, and (3) normotension. Stool, urine, and serum samples were collected in fasting conditions. Gut microbiota was characterized by 16S amplicon sequencing. Metabolomics, including quantification of short-chain fatty acids was conducted using nuclear magnetic resonance. Two-way ANOVA combined with Tukey post hoc test, as well as multiple permutation test and Benjamini-Hochberg-Yekutiel false discovery rate procedure, was used. The cohort included 54 males: 38 hypertensive (including 21 under treatment), 7 borderline, and 9 normotensive. No significant difference was observed between groups concerning age, body mass index, smoking habits, and weekly alcohol consumption. The genus Clostridium sensu stricto 1 positively correlated with BP levels in non-treated patients (n=33). This correlation was significant after multiple permutation tests but was not substantiated following false discovery rate adjustment. Short-chain fatty acid levels were significantly different among groups with higher stool levels of acetate, butyrate, and propionate in hypertensive versus normotensive individuals. No difference was observed in serum and urine metabolomes. Correlation between stool metabolome and 24-hour BP levels was evidenced, with R(2) reaching 0.9. Our pilot study based on 24-hour ambulatory BP measurements, 16S amplicon sequencing, and metabolomics supports an association between gut microbiota and BP homeostasis, with changes in stool abundance of short-chain fatty acids.
Abstract

Gut microbial metabolites have been implicated in contributing to blood pressure regulation; however, only a few microbial metabolites have been examined to date. In this study, we hypothesized that an unbiased screen for changes in gut microbial metabolites in a chronic Ang II (angiotensin II) infusion model would identify novel microbial metabolites associated with blood pressure regulation. To accomplish this, we used both conventional and germ-free mice, which had been implanted with minipumps to infuse either saline or Ang II. Our aim was to identify metabolites that were altered with Ang II treatment in conventional mice, but not in germ-free mice, indicating that they are dependent on the gut microbiota. Both plasma and feces samples were processed and analyzed using liquid chromatography-tandem mass spectroscopy. In plasma, we identified 4 metabolites that were significantly upregulated and 8 metabolites that were significantly downregulated with Ang II treatment in conventional mice; none of these metabolites changed in germ-free mice. Similarly, in feces, we identified 25 metabolites that were significantly upregulated and 71 metabolites that were significantly downregulated with Ang II treatment in conventional mice; none of these metabolites changed in germ-free mice. Finally, fecal 16S sequencing revealed significant shifts in the microbiome of conventional mice with Ang II treatment, including sex-specific changes. These data demonstrate that the metabolites that are differentially regulated with Ang II are dependent on the gut microbiome.

Gut Microbiota Composition and Blood Pressure

Abstract

Animal models support a role for the gut microbiota in the development of hypertension. There has been a lack of epidemiological cohort studies to confirm these findings in human populations. We examined cross-sectional associations between measures of gut microbial diversity and taxonomic composition and blood pressure (BP) in 529 participants of the biracial (black and white) CARDIA (Coronary Artery Risk Development in Young Adults) study. We sequenced V3 to V4 regions of the 16S ribosomal RNA marker gene using DNA extracted from stool samples collected at CARDIA’s Year 30 follow-up examination (2015–2016; aged 48–60 years). We quantified associations between BP (hypertension [defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or antihypertension medication use] and systolic BP) and within and between-person diversity measures. We conducted genera-specific multivariable-adjusted regression analysis, accounting for multiple comparisons using the false discovery rate. Hypertension and systolic BP were inversely associated with measures of alpha-diversity, including richness and the Shannon Diversity Index, and were distinguished with respect to principal coordinates based on a similarity matrix of genera abundance. Several specific genera were significantly associated with hypertension and systolic BP, although results were attenuated with adjustment for body mass index. Our findings support associations between within-person and between-person gut microbial community diversity and taxonomic composition and BP in a diverse population-based cohort of middle-aged adults. Future study is needed to define functional pathways that underlie observed associations and identify specific microbial targets for intervention.

Potential Influences of Gut Microbiota on the Formation of Intracranial Aneurysm

Abstract

Gut microbiota modulates metabolic and immunoregulatory axes and contributes to the pathophysiology of diseases with inflammatory components, such as atherosclerosis, diabetes, and ischemic stroke. Inflammation is emerging as a critical player in the pathophysiology of an intracranial aneurysm. Therefore, we hypothesized that the gut microbiota affects aneurysm formation by modulating inflammation. We induced intracranial aneurysms in mice by combining systemic hypertension and a single injection of elastase into the cerebrospinal fluid. Depletion of the gut microbiota was achieved via an oral antibiotic cocktail of vancomycin, metronidazole, ampicillin, and neomycin. Antibiotics were given 3 weeks before aneurysm induction and either continued until the end of the experiment or stopped 1 day before aneurysm induction. We also assessed the effects of the gut microbiota depletion on macrophage infiltration and mRNA levels of inflammatory cytokines. Gut microbiota depletion by antibiotics reduced the incidence when antibiotics were started 3 weeks before aneurysm induction and continued until the end of the experiment (83% versus 6%, P<0.001). Even when antibiotics were stopped 1 day before aneurysm induction, the gut microbiota depletion significantly reduced the incidence of aneurysms (86% versus 28%, P<0.05). Both macrophage infiltration and mRNA levels of inflammatory cytokines were reduced with gut microbiota depletion. These findings suggest that the gut microbiota contributes to the pathophysiology of aneurysms by modulating inflammation. Human studies are needed to determine the exact contribution of the gut microbiota to the pathophysiology of aneurysm formation and disease course in humans.
ARTICLE INFORMATION

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Disclosures
None.

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