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Gut dysbiosis and hypertension – is it cause or effect?

Katherine L. Cook, PhD, **Mark C. Chappell, PhD, FAHA**

Hypertension & Vascular Research Center, Wake Forest University School of Medicine, Winston-Salem, NC USA

The worldwide incidence of hypertension is at pandemic proportions with an estimated one in six adults exhibiting a sustained elevation in blood pressure (1). Hypertension remains the leading risk factor for cardiovascular disease (CVD) in both men and women; however, the underlying mechanisms of the disease remain obscure (1). The current treatment approaches for hypertension constitute pharmacological regimens targeting the renin-angiotensin-aldosterone system (RAAS) - angiotensin converting enzyme (ACE), the angiotensin type 1 receptor (AT1R), the aspartyl protease renin, and the mineralocorticoid receptor (MR), adrenergic receptors of the sympathetic nervous system, various renal sodium transporters and vascular calcium channels. Adequate control of blood pressure in hypertensive patients typically requires multiple treatment regimens; however, it is also estimated that blood pressure is well-controlled in less than 50% of those patients with hypertension which may reflect, in part, the influence of co-existing cardiovascular risk factors including obesity, atherosclerosis and insulin resistance, as well as the multiple systems that contribute to the mosaic of hypertension (1,2). In lieu of the efficacy of current anti-hypertensive treatments, there is extensive interest in the role of the gut microbiome on the development of hypertension and other cardiovascular pathologies. Certainly, the recognition that the microbiome constitutes a far greater extent of cellular and genetic material than that of our own cells and that the biome serves a key role in maintaining nutritional and immune homeostasis underlies the current focus. Indeed, evidence to date suggests that alterations in the gut microbiota (dysbiosis) are associated with hypertension in patients and in several preclinical models (1–5). Moreover, fecal material transfer (FMT) from hypertensive patients including preeclamptic women is associated with an increase in blood pressure and inflammation in germ-free murine recipients suggesting a mechanistic role of the gut biome (6, 7). In this regard, Raizada and colleagues (8) propose that gut dysbiosis is a causative factor in the development of hypertension that may arise from enhanced sympathetic tone, reduced mesenteric blood flow and an increased systemic inflammation. This stimulated inflammatory system may reflect alterations in the junction of epithelial cells (leaky gut) that lead to increased permeability of the endotoxin lipopolysaccharide (LPS), a membrane component of gram negative bacteria that comprise the majority of gut bacteria, as well as other pathogen-associated molecular

Address for Correspondence: Mark C. Chappell, PhD, FAHA, Professor, Hypertension & Vascular Research Center, Wake Forest University School of Medicine, Biotech Place, 575 Patterson Ave., Winston-Salem, NC 27101, Telephone: 336-716-9236, Fax: 336-716-2456, mchappel@wakehealth.edu.

DISCLOSURES

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patterns (PAMPs) that stimulate toll-like receptors such as TLR-2 and TLR-4 (2–4). The overall balance of the gut microbiota composition may also influence the regulation of blood pressure. Reduced abundance of *Lactobacillus* species is associated with hypertension and may reflect a deficit in the generation of *Lactobacillus*-derived peptides that exhibit ACE inhibitory activity (5). Attenuated ACE activity would reduce Ang II levels and activation of the AT1R axis, but also promote greater expression of the vasodilatory and anti-inflammatory peptide Ang-(1–7). Oral administration of Ang-(1–7) expressed in the probiotic *Lactoacbaccilus paracasei* markedly increased the circulating levels of the peptide that was associated with improved indices of microbiome diversity in aged Fisher 344 rats, particularly an increase in the anti-inflammatory species *Akkermansia muciniphila,* also linked to the integrity of the gut barrier (9). Additionally, certain microbiota species generate short-chain fatty acids (SCFAs) including propionate, succinate and butyrate (2–4). The production of butyrate may be protective to the cardiovascular system as this SCFA exhibits anti-inflammatory properties that may reflect the inhibition of histone deacetylase (HDAC) activity (4). SCFAs may also have beneficial effects by stimulating specific fatty acid receptors (FFAR) that have direct vasodilatory effects or may stimulate FFARs on vagal afferents in the gut to elicit parasympathetic pathways in the brain to lower pressure that may be the basis for a microbiome gut-brain axis to regulate blood pressure (3,8). Indeed, in a clinical study of overweight and obese pregnant women, blood pressure was inversely associated with butyrate-producing gut microbiota populations giving further evidence suggesting the antihypertensive role of bacterial-generated SCFA (10).

A key issue regarding the role of the microbiome in hypertension and other cardiovascular pathologies is whether gut dysbiosis is a causative insult leading to a sustained increase in blood pressure or that hypertension impacts the microbiome to an extent that the altered microbiota contributes to the progression and/or continued hypertensive state. Konopelski et al. (11) address this issue in a crossed fecal microbiota transplant (FMT) study between an experimental model of primary hypertension in the spontaneously hypertensive rat (SHR) and the Wistar Kyoto (WKY) rat as the normotensive control group. The underlying mechanism(s) for the increase in blood pressure in this genetic model of hypertension remains undefined, and the SHR is considered a relevant model of human primary hypertension. This study performed colonic transplant of fecal content from male SHR or WKY into each recipient group (SHR FMT to WKY$_{SHR}$; WKY FMT to SHR$_{WKY}$) pre-treated with the broad spectrum antibiotic neomycin to clear the host biome and blood pressure was continuously monitored by telemetry (11). Controls included both WKY and SHR groups that received corresponding FMT (WKY to WKY$_{WKY}$ and SHR to SHR$_{SHR}$) to account for all surgical procedures. Fecal material was obtained from 14 week-old donor rats and colonic transplants performed in 9 week-old recipients. In the SHR at 9 weeks of age, blood pressure continues to increase, but pressure is well-established and plateaus by 14 weeks of age. Apart from differences in body mass, blood pressure and microbiota species, a number of metabolic parameters were similar between the 14-week old donor SHR and WKY groups (11). Assessment of the FMT on blood pressure was analyzed by telemetry instrumented in animals 2 weeks prior to the fecal transplant to allow for normalization of the pressure analysis and hemodynamic measurements continued for 7 weeks. The difference in systolic blood pressures between the SHR and WKY groups were ~60 mmHg

by the end of the experimental period with the SHR group exhibiting a ~20 mmHg increase in pressure from 7 to 14 weeks of age (11). Surprisingly, there was no effect of the donor WKY FMT to lower blood pressure in the SHR recipients or the donor SHR FMT to elevate blood pressure in the WKY recipients. The study also revealed no differences in the diurnal variation of blood pressure among the FMT treated SHR and WKY groups. Transfer of WKY fecal material into SHR did not improve the histology of the colonic mucosa (lower mucosal height), the reduced number of goblet cells nor the increased number of infiltrating lymphocytes assessed at the end of the study. Conversely, SHR fecal transfer to WKY did not convey an adverse effect on these parameters of inflammation or the colonic architecture. The SHR exhibited greater alpha diversity (higher number and diversity of microbiota species) than WKY; however, FMT did not affect these differences in either the SHR_{WKY} or WKY_{SHR} treatment groups (11). Interestingly, pre-hypertensive and hypertensive patients typically exhibit *reduced* microbiota diversity and number as compared to normotensive controls (5).

The authors conclude that gut dysbiosis in the SHR likely constitutes a consequence of the hypertensive phenotype rather than a causative outcome by the microbiome on the development and progression of hypertension (11). Moreover, fecal transfer did not significantly impact the host's microbiota or indices of colon health in either the SHR or WKY. The current study conflicts with earlier reports that FMT from hypertensive donors increased blood pressure in normotensive recipients or that the normotensive host FMT reduced pressure in the hypertensive recipient (6–8, 12–14). Apart from an elevated blood pressure, Toral et al. (12) reported that FMT from male SHR was associated with indices of oxidative stress and inflammation in the brain paraventricular nucleus (PVN), as well as circulating levels of LPS in the WKY recipients. In a companion study, blockade of T-cell activation by CTLA4-Ig abolished the hypertensive response and corrected the vascular dysfunction induced by SHR FMT in the WKY recipient (13). Similar effects on blood pressure and vascular dysfunction were also evident following administration of an IL-17 neutralizing antibody (13). Overall, these two studies suggest a strong link between the microbiome and inflammation to induce hypertension that parallels the SHR phenotype, although the mechanism for T-cell activation was not defined. Toral et al. (12, 13) assessed blood pressure by tail-cuff measurement and utilized older male SHR and WKY (25 week-old) that were gavaged weekly over a 4 week period from younger 20 week-old donors. Adan et al. (14) also reported that donor FMT from stroke-prone SHR (SP-SHR, 19 week-old) elicited a hypertensive response in WKY recipients that were gavaged weekly from 6.5 to 16.5 weeks of age; while donor WKY FMT (9 week-old) tended to lower blood pressure in SHR but did not reach statistical significance; blood pressure responses were again measured by tail-cuff plethysmography (14) Surprisingly, the Adan study (14) did not assess the effects of FMT in WKY_{SHR} or $SP\text{-}SHR_{WKY}$ on blood pressure or other cardiovascular indices. It is difficult to reconcile the findings of these latter studies with the current report, although the age of the donor and recipient rats were different and potential strain differences in SHR and WKY may contribute (15), as well the assessment of blood pressure (tail-cuff vs. telemetry) in which telemetry may obviate stress-induced effects by the tail-cuff procedure. The administration of fecal material to repopulate the recipient biome also differed between these studies. The Toral and Adan studies (12–14) gavaged

animals weekly for 4 and 10 weeks, respectively, that was associated with significant changes in the recipients' biome, while Konopleski et al (11) applied donor material directly into the colon twice over a 24 hour period that failed to induce gut dysbiosis in the recipient WKY or SHR at the end of the 7 week study in which there were no changes in blood pressure at any time point. The rationale for colonic FMT is this approach parallels fecal transplant in patients for treatment of recurrent Clostridiodes difficile that restores the recipient biota, although cecal and ilial administration with loperamide (to prolong FMT exposure) is further recommended in these patients (16). However, colonic FMT in the current study likely failed to impact the upper gastrointestinal system including the cecum which constitutes a more enlarged area of the rat ilium to facilitate metabolism of their dietary grain intake. Additionally, the frequency of colonic FMT may not have been sufficient to induce long-term changes in the gut biome of the SHR and WKY recipients to influence blood pressure and other cardiovascular indices.

In conclusion, the present findings found no effect of fecal material from genetically hypertensive rats to elicit a sustained increase in blood pressure in the normotensive recipient nor that the biome from normotensive donors reduced blood pressure in hypertensive recipients. These findings conflict with earlier studies that FMT influences blood pressure and the host biome; however, the frequency and route of fecal material administration may account for these disparate findings rather than a primary influence of the hypertensive or normotensive host on the transplanted biome. Not unexpectedly, the study raises additional questions on the functional role of the gut microbiome in hypertension and cardiovascular disease, particularly the cardiovascular consequences to chronically influence the host biome. Finally, this study emphasizes the lack of data in estrogen-intact or estrogen-depleted females as the majority, if not all preclinical experimental studies (with the possible exception of preeclampsia models) on the cardiovascular actions of the gut biome have been performed in males (5).

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