Autophagy and Hypertension-Associated Premature Vascular Aging

CAMERON MCCARTHY

University of Toledo College of Medicine and Life Sciences,
Toledo, USA.

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Many of the pathophysiological changes that occur in hypertension are the result of an accelerated deterioration in organ function, similar to what is observed in aging. While the increased incidence of cardiovascular events as we age is generally attributable to the natural decline in organ function, in hypertension, organ dysfunction is premature in its onset and particularly pronounced, especially in the vasculature¹. In fact, arteries from hypertensive patients and animals present a range of phenotypes including, hypercontractility, stiffening and remodeling, inflammation, and oxidative stress, that a relatively early in there onset compared to age-matched normotensive controls. As a result, vascular age determination, as opposed to chronological age *per se*, has now been introduced into clinical guidelines for cardiovascular disease prevention. Nonetheless, a critical barrier to our progress in reducing the morbidity and mortality of hypertensive patients is our lack of understanding of the precise mechanisms that underlie premature vascular aging.

The aged phenotype is classically viewed as the accumulation of damaged cellular debris and dysfunctional organelles. Although waste products are an inevitable consequence of normal cellular metabolism, multiple systems are devoted to its repair, clearance, or recycling. Autophagy is the evolutionarily conserved catabolic process essential for both maintaining homeostasis via the recycling and removal of damaged cellular debris and dysfunctional organelles, as well as to provide micronutrients during times of starvation and stress.

Autophagy has long been associated with longevity, including the lengthening of lifespan². Therefore, it is plausible that a decline in autophagy contributes to premature vascular aging in hypertension. This notion is supported by studies that showed that an upregulation of autophagy reversed several

phenotypes of vascular aging in old mice, including endothelial function³. Moreover, our own previous data have reported that autophagic activity is reduced in resistance and conduit arteries from spontaneously hypertensive rats (SHR), and that reconstitution of autophagy ameliorated endothelial function and arterial stiffness in SHR⁴.

Precisely how autophagy induction reduces the aged vascular phenotype (both chronological vascular aging and premature vascular aging associated with hypertension) is the focus of intense and rigorous research⁵. Until now, many of the important discoveries are centered on the premise that reduced autophagy leads to the accumulation of damaged cellular debris and dysfunctional organelles that causes inflammation and oxidative stress. Subsequently, this pro-inflammatory/pro-oxidative milieu quenches nitric oxide bioavailability. Therefore, upregulation/reconstitution of autophagy decreases these vascular dysfunctions. While these rigorous investigations have provided an important phenotypic understanding of how autophagy can ameliorate vascular function and structure in aging and hypertension, most of these studies have attempted to upregulate autophagy in the vasculature directly by using systemic interventions (e.g., lifestyle modifications, pharmacological agents administered orally, or transgenic overexpression). Therefore, these studies cannot rule out the contribution of multiple organ systems contributing to the vascular phenotypes measured.

Given the close association of autophagy with metabolic homeostasis, it is plausible that upregulation of autophagy imparts influence on metabolic pathways in diverse organs such as the liver and adipose tissue, as well as in endothelial and vascular smooth muscle cells. Catabolism of metabolic substrates via autophagy would therefore lead to the generation of novel

metabolites that can elicit anti-hypertensive and anti-vascular aging effects.

In summary, the generation of autophagy-dependent metabolites, especially from extravascular depots, proposes both a physiological mechanism by which autophagy can prevent vascular aging, and a pathogenic mechanism of decreased autophagy in hypertension. Moreover, these mechanisms incorporate the known anti-hypertensive and vasculoprotective effects of intermittent fasting and exercise, given that both lifestyle interventions are known stimulators of autophagy.

References:

1. Taddei S, Virdis A, Mattei P, Ghiadoni L, Fasolo CB, Sudano I, Salvetti A. Hypertension causes premature aging of endothelial function in humans.

Hypertension. 1997;29:736-743. DOI: [10.1161/01.hyp.29.3.736](https://doi.org/10.1161/01.hyp.29.3.736)

2. Pyo JO, Yoo SM, Ahn HH, Nah J, Hong SH, Kam TI, Jung S, Jung YK. Overexpression of Atg5 in mice activates autophagy and extends lifespan. Nat Commun. 2013;4:2300. DOI: [10.1038/ncomms3300](https://doi.org/10.1038/ncomms3300)

3. LaRocca TJ, Henson GD, Thorburn A, Sindler AL, Pierce GL, Seals DR. Translational evidence that impaired autophagy contributes to arterial ageing. J Physiol. 2012;590:3305-3316. DOI: [10.1113/jphysiol.2012.229690](https://doi.org/10.1113/jphysiol.2012.229690)

4. McCarthy CG, Wenceslau CF, Calmasini FB, Klee NS, Brands MW, Joe B, Webb RC. Reconstitution of autophagy ameliorates vascular function and arterial stiffening in spontaneously hypertensive rats. Am J Physiol Heart Circ Physiol. 2019;317:H1013-H1027. DOI: [10.1152/ajpheart.00227.2019](https://doi.org/10.1152/ajpheart.00227.2019)

5. Nussenzweig SC, Verma S, Finkel T. The role of autophagy in vascular biology. Circ Res. 2015;116:480-488. DOI: [10.1161/CIRCRESAHA.116.303805](https://doi.org/10.1161/CIRCRESAHA.116.303805)

Cameron McCarthy - cameron.mccarthy@utoledo.edu

COMMITTEE REPORT

Research and Education Committee Goes Global

NADIA KHAN

University of British Columbia, Centre for Health Evaluation & Outcomes Sciences, Vancouver, British Columbia, Canada.

With the pandemic, the world has undergone a seismic shift in research and education. Research programs, work in scientific labs and clinical trials came to a halt and educational opportunities such as conferences were deferred or cancelled. Despite these impacts on research and education, new opportunities and lessons emerged. First, we bore witness to unprecedented, ultra-rapid development of vaccines and the development and testing of novel clinical treatments for COVID-19 infections made possible through advanced technologies and concentrated global efforts on a singular issue. In our first virtual ESH/ISH conference, over 5000 attendees and speakers from all over the world were able to access high quality educational sessions without leaving their homes and offices.

Harnessing global, diverse talent and leveraging the now commonplace technologies for communication, can multiply the Society's impact and reach on hypertension research and education. In developing our committee's aims and mandate to encourage the advancement of scientific research and knowledge globally, we aimed to use virtual platforms and partner with diverse, talented researchers and hypertension leaders globally. The committee also listened to the ISH member's input asking to help promote member's research and provide greater opportunities to participate in impactful knowledge outputs from the Society.

Prior to my role as chair of the Committee, I served as a council member and on the Women