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High Salt and IL-17 in Aortic Dissection

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Aortic dissection (AD) is defined as tearing of the aortic wall, a disease that results in high mortality due to aortic rupture and malperfusion.[1] Unfortunately, the current available techniques cannot predict the onset of AD. Therefore, understanding the pathophysiology and mechanisms of AD is in a dire medical need. In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, an elegant publication by Nishida *et al.* reported that high salt intake augmented AD through an interleukin-17 (IL-17)-dependent mechanism (Figure 1).[2]

Many studies have reported that high salt intake is associated with cardiovascular diseases including hypertension and aortic aneurysms.[3–8] Although hypertension is a risk factor for AD,[9] the impact of high salt intake on AD formation has not been investigated. The study by Nishida *et al*. revealed adverse effects of high salt intake on AD induced by subcutaneous co-infusion of angiotensin II (AngII) and β-aminopropionitrile monofumarate (BAPN).[2] The authors performed detailed characterization on histological features of medial disruption and aortic rupture. They subsequently demonstrated that increased salt intake led to augmentation of the aortic pathology (Figure 1).

In the study of Nishida *et al*,[2] salt (1% wt/vol NaCl) was provided in drinking water. In humans, high salt intake is due to excessive salt in diet, in contrast to the drinking water that was the delivery mode in this study. A recent human study demonstrated that high salt intake (12 g/day) in food increased urinary cortisol and cortisone excretions, and changed catabolic hormone profile.[10] In contrast, a diet containing high salt (4% wt/wt NaCl) fed to mice with ad libitum access to water did not alter urinary glucocorticoid concentrations or catabolic state.[11] However, combination of a 4% wt/wt NaCl diet and isotonic saline (0.9% wt/vol) in drinking water increased urinary glucocorticoid excretion and recapitulated the catabolic

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Disclosures

None.

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hormone profile change observed in the human study.[10, 11] Thus, in mouse studies, the route of salt administration is critical for elucidating effects of high salt intake. Salt administered in drinking water, as reported by Nishida et al.,[2] can mimic the human response to high salt loading.

AD exhibits disruption of the intima and medial layers of the aorta with intramural hematoma that forms a false lumen.[9] These features were also detected in mice infused with AngII and BAPN.[12, 13] In the study by Nishida *et al.*[2], AD was described as an intramural hematoma with greater diameters (> 1.5-fold) than the external diameter at the distal site of the corresponding aortic region (used as the reference diameter). This criterion to define AD formation was based on the authors' previous report that progression of medial disruption was associated with formation of intramural hematoma and increased aortic diameter.[14] On the basis of these definitions, the authors found that high salt administration exacerbated AD induced by co-infusion of AngII and BAPN. In addition to the incidence, the authors used length of lesions with aortic wall destruction to represent AD severity. End-organ ischemia due to dissection-related obstruction of aortic branch vessels is a deleterious consequence of AD and is associated with higher mortality.[9] Since longer AD lesions have higher risk for complicating perfusion to branch vessels, lesion length is an optimal parameter to determine AD severity. However, it is unclear whether short lesions would be associated with lower incidence of aortic rupture. Therefore, multiple parameters may need to be considered in order to predict aortic rupture.

To investigate mechanisms by which high salt intake exacerbated AD, the authors[2] explored IL-17 signaling pathway. IL-17 is a cytokine secreted from helper T lymphocytes (Th17) that was increased in AD tissues,[15, 16] and high salt intake increased Th17 lymphocytes and inflammation.[15] These findings support potential links among high salt intake, IL-17, and AD formation. Indeed, whole body deletion of IL-17 reduced high salt-accelerated AD incidence and severity, whereas deletion of IL-17 had no effects on AD in mice with normal salt intake (mice were given only normal drinking water).[2] This study therefore provides a mechanistic insight into linking high salt intake and AD augmentation through IL-17 signaling pathway (Figure 1).[2] Salt intake regulates the renin-angiotensin-aldosterone system.[17] There has been consistent evidence that this hormonal system contributes to aortopathies.[18] Therefore, it would be also interesting to determine the regulation of the renin-angiotensin-aldosterone system in high salt induced augmentation of AD.

A frequent approach for exploring mechanisms is to compare the abundance of components between normal and diseased tissues. However, this approach does not discriminate whether the differences are a consequence of the pathology or the cause. To overcome this common shortcoming, Nishida *et al.*[2] harvested aortic samples at early phase (3 days of infusion) prior to AD development. A spectrum of changes were noted between mice given normal versus high salt, including alterations of IL-17 receptor and TGF-β signaling, collagen deposition, and aortic force displacement. Since these parameters were altered prior to detecting overt pathologies, they may represent causative mechanisms. AD is initiated by disruption of the intima that consequently tears medial layers.[9] Therefore, aortic pathologies, including aortic dilatation and intramural hematoma, are consequences of this initial disruption.[9] It is important to define the entry site of blood in AD. Nishida *et al.*[2] performed

detailed histological anaysis from the intact proximal region throughout the diseased region, providing insights into the complex AD pathology.

The study by Nishida *et al.*[2] provides solid evidence that high salt intake plays a critical role in augmenting AD formation through IL-17 signaling pathway. We look forward to future studies that examine the effect of salt restriction, as a potential therapeutic strategy, on AD formation and mechanisms beyond IL-17 and its signaling pathway.

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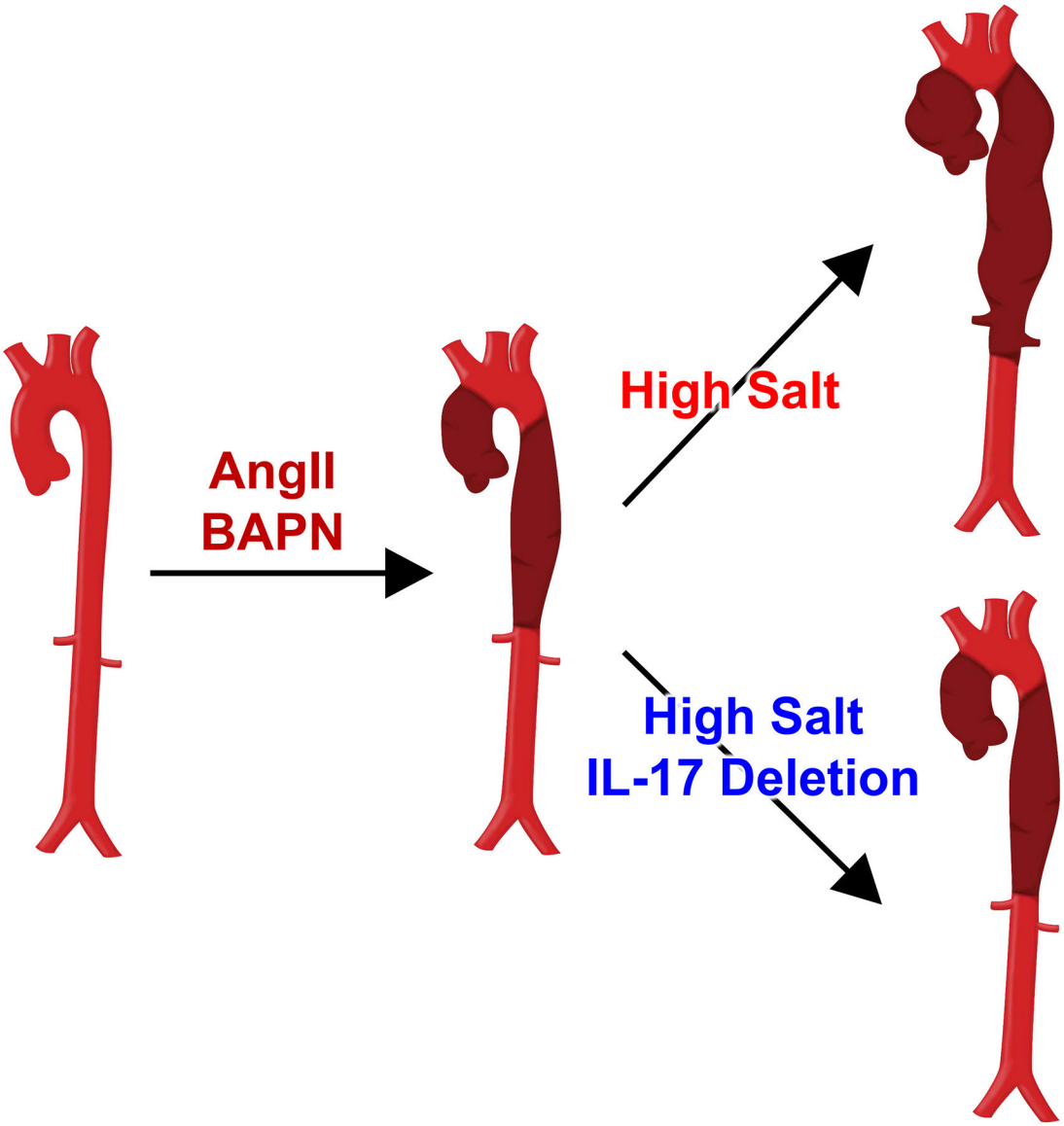

Figure 1. Schematic summary of the findings reported by Nishida et al.[2]

Administration of angiotensin II (AngII) and β-aminopropionitrile (BAPN) leads to focal aortic dissection in thoracic and abdominal aortic regions in mice with normal salt intake. High salt intake leads to more extensive pathological changes in mice administered AngII and BAPN. Whole body interleukin-17 deletion diminishes high salt-induced augmentation of aortic dissection.