REVIEW

Effect of hypertension on the natural history of intracranial aneurysms

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ABSTRACT

Intracranial aneurysm (IA) is a cerebrovascular disease characterized by localized structural deterioration and an arterial wall bulge. It can remain asymptomatic for many years or rupture suddenly with life-threatening results. Hypertension is one of the most common risk factors and complications of IAs. Despite advances in treatment philosophy and perioperative management, many unknowns remain about IA's natural history. In addition, numerous studies have shown hypertension's impact on the IA formation, development, and rupture process. In this review, we summarize the current understanding of hypertensive mechanisms in IA patients to identify those potentially contributing to IAs for future research. (Am J Transl Med 2022. 6(4):156-166).

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INTRODUCTION

Intracranial aneurysms (IAs) affect up to 7% of the human population and have an approximately ~1% rupture rate, the most common cause of spontaneous subarachnoid hemorrhage (SAH) associated with high morbidity and mortality (Zheng et al., 2021).

The actual causes of IA remain unknown. However, its risk factors can be divided into two groups: unmodifiable factors, such as age and sex, and modifiable factors, such as hypertension and smoking. A study using The Nationwide Inpatient Sample database showed that despite a decreasing trend in annual aneurysmal SAH (aSAH) hospitalizations due to lifestyle modifications and treatment advances,

hypertension continues to increase in prevalence among patients with aSAH by 1.60% annually (Wahood et al., 2022). Therefore, controlling this modifiable risk factor could significantly reduce aSAH's social burden.

Many human and experimental studies have shown that hypertension contributes to IA occurrence, development, and rupture. However, some recent studies showed that hypertension is not associated with IA's natural history. Instead, sudden blood pressure changes and poor blood pressure control contribute to these processes. High blood pressure is a complex, highly coordinated process involving inflammatory response, blood dynamics, and genetic factors. Therefore, they are also significant factors in evaluating IA development and prognosis.

Therefore, some controversies exist about hypertension's effects on IA, indicating that its mechanism remains unclear. Moreover, patient survival rates and prognoses could be greatly improved by a better understanding of modifiable risk factors such as hypertension and their appropriate control before or during IA development or rupture.

While existing studies on hypertension or blood pressure control have been extensively reviewed, few articles have reviewed current mechanisms and treatments in different IA stages. In this review, we discuss hypertension's role in IA's natural history and attempt to identify potential appropriate interventions to decrease IA development and rupture through better blood pressure control management.

HYPERTENSION DURING IA OCCURRENCE AND DEVELOPMENT

Increasing evidence consistently indicates that hypertension is a significant factor in IA pathogenesis. Most IAs originate from anatomical variations caused by genetic factors, such as hypoplasia or fenestration, at the circle of Willis' branch arteries, which are connected to the branch Angle (Bor, Velthuis, Majoie, & Rinkel, 2008). This phenomenon provides an aneurysm with its structural underpinnings. Hypertension is one factor initiating aneurysm formation. Chronic hypertension causes reactive lipohyalinosis, smooth muscle cell hypertrophy and damage within the vessel wall, vascular contractility loss, and cerebral autoregulation due to type IV collagen fiber deposition.

Cerebral blood flow is tightly regulated to ensure adequate cerebral blood perfusion through cerebral autoregulation with a wide fluctuating systemic blood pressure range between 60 and 160 mmHg. Cerebral perfusion pressure (the difference between mean systemic arterial blood pressure and intracranial pressure) is normally relatively constant (Hasan et al., 2015). Much experimental and human research evidence supports hypertension's significant role in IA development (Hosaka et al., 2014). Hemodynamics, inflammatory reactions, the renin-angiotensin system (RAS), blood pressure fluctuation, and hereditary factors comprise most of the response and the associated reaction in hypertension.

HEMODYNAMIC STRESS

The IA is directly affected by the flow from the parent atrial and aneurysm sac, whose hemodynamics changes vary by systemic pressure.

Systolic pressure differences between intracranial parent arteries and aneurysms were approximately 3–5 mmHg. Previous research has shown a close linear relationship between systemic arterial and intra-aneurysmal pressure changes. However, differences in diastolic and mean radial, parent artery, and aneurysm pressures were nonsignificant in all locations. This study used the phenylephrine infusion method to reach 25 mmHg above baseline as its hypertension target. It showed that absolute differences in systolic pressures (SBPs) between the intra-aneurysmal and systemic arteries were 14–19 mm Hg at target radial pressures, compared with 7–11 mmHg at baseline radial pressures (Hasan et al., 2015). Therefore, hypertension patients

may have an excessive increase in pressure during aneurysms. However, SBP and mean pressures were consistently greater in the aneurysm than in the radial artery, partly attributed to greater vascular stiffness. Changes in peak and mean flow velocities were nonsignificant in parent arteries. This phenomenon is consistent with the autoregulation mechanism of intracranial vessel flow.

Consequently, blood pressure is a convenient indicator of parent artery and IA hemodynamics. Moreover, hypertension fundamentally affects IA development, which has been confirmed in animal models.

The first experimental animal model study of aneurysms used hypertension and flow velocity to induce hemodynamic stress, creating the first rodent cerebral aneurysm model in rats (Yong-Zhong & van Alphen, 1990). While this model had a relatively low success rate for inducing aneurysms, it indicated that the hemodynamic mechanism caused by hypertension was important in aneurysm formation. This animal IA model was continuously improved to increase successful aneurysm formation. In a modified murine IA model, mice on a hypertensive diet had their left common carotid and right renal arteries ligated and were given elastase solution and angiotensin II (Hosaka et al., 2014). In a rabbit IA model, hypertensive rabbits had more widespread flow-induced aneurysmal damage and greater vessel length and tortuosity increases after carotid ligation than after ligation alone. Additionally, it did not affect overall vessel caliber enlargement, which may have occurred as a compensatory reaction to reestablish proper blood distribution when the carotid arteries were blocked (Tutino et al., 2015).

A meta-analysis examined research findings contrasting geometrical cerebral aneurysm and "aneurysmal lesion" models in which aneurysms were surgically excised. It found that aneurysm formation may be influenced by high wall shear stress and increased gradient oscillations (Han et al., 2021). Increased wall tension on arterial wall remodeling and increased flow and subsequent wall shear stress predisposing to aneurysm formation are two potential mechanisms for saccular IA formation. In both mechanisms, hypertension affects artery wall remodeling related to aneurysm initiation (Räisänen et al., 2022).

INFLAMMATORY RESPONSES

Hypertension interacting with several cytokines and inflammatory mediators contributes to IA pathogenesis. Collagen type I, the aneurysm wall's main molecular constituent, could be considered a collagen biosynthesis and turnover indicator in IA. Several studies have shown that collagen type I manifested < 5 years old and had a 126% mean collagen turnover rate (γ) annually in IA. For patients with modifiable risk factors, such as hypertension, γ was >2600% annually, compared with 32% in patients without a history of risk factors (Etminan et al., 2014). Moreover, collagen from IA in patients was significantly younger in those with risk factors (mean = 1.6 ± 1.2 years) than without risk factors (mean = 3.9 ± 3.3 years; $P = 0.012$) (Hackenberg et al., 2020). Immature collagen remodeling and chronic histological development in the IAs of hypertensive patients with greater collagen γ are significantly associated with their modifiable risk factor history.

The SRY-box transcription factor 17 (*SOX17*) is expressed in the endothelial cells of normal intracerebral vessels. Angiotensin II injection and *Sox17* loss resulted in cerebral vascular reconstructions in mouse models, generally matching IA hallmarks by causing vessel enlargement, wall thinning, and tortuosity. In intracranial arteries, these reactions impaired junctional assembly, cell-matrix adhesion, regeneration potential, and paracrine secretion, showing severe endothelial dysfunctions contributing to IA pathogenesis. *Sox17* deficiency affected IA formation in rats with hypertensive diseases (Lee et al., 2015). Functionally relevant polymorphisms in inflammatory-related cytokine genes have been analyzed in IA patients. They suggested that stochastic interleukin 10 (IL10) and transforming growth factor beta 1 (TGFB1) response regulation may promote IA's natural history under hypertension conditions through vascular matrix

degradation, followed by chronic responses to inflammatory cytokines such as tumor necrosis factor (TNF/TNFα) and interferon-gamma (IFNG). These interactions between genetic variants and specific comorbid factors contribute to understanding phenotypic variation in IA pathogenesis (Sathyan et al., 2015).

Many studies have shown the inflammation responses' role in IA's natural history. However, these basic research studies focused mainly on the mechanism of cellar transcription factors and inflammatory mediators, and the effect of inflammation on IA pathogenesis in clinical trials remains unclear. One study explored whether using anti-inflammatory drugs reduced neonatal aneurysms in saccular IA patients. It found that patients taking regular prostaglandin-endoperoxide synthase 2 (PTGS2/COX2) selective inhibitors had a smaller rate of de novo aneurysm (1.1% vs. 3.6%). However, taking acetylsalicylic acid and other pharmaceutical COX2 inhibitors was not a significant neonatal IA indicator.

In contrast, IA risk was influenced by modifiable risk factors such as smoking or irregular antihypertensive therapy. Indeed, managing risk factors such as smoking and hypertension appeared more significant than using COX2 selective inhibitors (Räisänen, Huttunen, Huuskonen, von Und Zu Fraunberg, Koivisto, Jääskeläinen, Lindgren, et al., 2022). Therefore, studies have examined whether intensive hypertension therapy with a target SBP of <120 mmHg combined with anti-inflammatory therapy with acetylsalicylic acid could reduce IA growth or rupture. The future outcomes of clinical trials may provide appropriate evidence for a treatment strategy for patients unsuitable for prophylactic surgical intervention (Vergouwen et al., 2018).

RENIN-ANGIOTENSIN SYSTEM

The RAS may also have a role in IA pathogenesis. Systemic hypertension affects pathological tissue reconstruction and the inflammatory response in the aneurysmal wall caused by its mechanical effects on abnormal hemodynamic stresses. It can also activate the local RAS in the vascular wall (Weiss & Taylor, 2008). Local RAS can control vascular reconstruction by activating smooth muscle migration and proliferation processes that could potentially degenerate the aneurysmal wall. In addition, it can mediate vascular inflammation by activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), further promoting inflammation inside the aneurysmal wall (Tada et al., 2014).

One study in estrogen-deficient rats on a high-salt diet found that raising the Na^+/water ratio increased cerebral aneurysm formation independent of hypertension (Matsushita et al., 2012). This study also found that additional bilateral oophorectomy or renal artery ligation in the bilateral oophorectomy group significantly increased the IA formation rate and Na^+/water ratio compared to the high-salt diet group. During the response, inflammation molecules (e.g., estrogen receptor 1 [*ESR1*/*ERα*], *TNF*, and *ATR1b*) were upregulated, and an ATPase subtype and *ATP1α2* were downregulated in the aneurysm wall. In contrast, using olmesartan, an angiotensin II receptor blocker, at a dose that did not affect blood pressure could reduce IA formation, Na^+ storage, and *ATP1α2* upregulation. In addition, another study found that a high-salt diet increased stroke risk in humans independent of its effect on the blood pressure (Li et al., 2012). Therefore, proper water-free Na^+ management may reduce IA formation, at least in rats (Matsushita et al., 2012).

Eplerenone, a mineralocorticoid receptor blocker, reduced molecules in the aneurysmal wall, including angiotensin I converting enzyme (ACE), reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits NADPH oxidase 4 (NOX4), nitrotyrosine, Rac family small GTPase 1 (RAC1), C-C motif chemokine ligand 2 (CCL2/MCP1), and matrix metalloproteinase 9 (MMP9). Decreases in these molecules showed that renin-angiotensin-aldosterone (RAAS) system suppression inhibits IA formation by reducing oxidative stress, inflammatory responses, local

RAS activation, and saline intake. Moreover, mineralocorticoid receptor agonist injection in other rats suggested an increased cerebral aneurysm formation rate and the upregulation of the above molecules. This study showed that mineralocorticoid receptor activation affected IA development (Tada et al., 2009).

Antihypertensive medication, especially angiotensin-converting enzyme inhibitors, affects aneurysm wall reconstruction by regulating inflammatory mediators and controlling blood pressure. However, few additional benefits from ACE inhibition were found compared with other antihypertensive medications (Räisänen, et al., 2022). This finding could be partly explained by one study that found decreased local RAS activation in saccular IAs based on a comparison between IA and the cortical cerebral artery in control patients (Ohkuma et al., 2003). They used reverse transcription-polymerase chain reaction and immunohistochemistry methods to assess local RAS levels. The outcome indicated that *AGTR1* and angiotensin II expression levels were higher in patients without than with hypertension. In addition, hypertension duration and gene polymorphisms in individuals may also affect the results. Indeed, the discrepancies between studies show that some unknown RAS mechanisms in hypertensive IA patients still require further exploration.

BLOOD PRESSURE VARIABILITY

It has been reported that visit-to-visit variability (VVV) in SBP is a strong predictor of stroke in patients with a history of transient ischemic attack (Rothwell et al., 2010). The clinical significance of VVV in SBP was higher than that of the mean SBP for the hypertensive heart disease (Masugata et al., 2011). One study found no discernible difference between the SBP of IA growth and unchanged patients. Nevertheless, the IA growth patients' VVV in SBP was noticeably larger than those of the unchanged patients, which was independently related to unruptured IA (UIA) growth. SBP variation (SBPV) is now widely acknowledged as a major risk factor in vascular disease. Several BPV metrics (coefficient of variation, successive variation, peak and trough sizes, and max/min) have been developed to measure variability. Indeed, SBPV affects vascular diseases more than mean SBP in several populations. Few studies have assessed SBPV's importance in SAH and how it can lead to aneurysm development (Rothwell et al., 2010). The causes of short-term, sharp fluctuations in blood pressure and arterial stiffness are two potential mechanisms for blood pressure variability. Age, sex, smoking, diabetes, and peripheral vascular disease were all associated with VVV in SBP, but only age and mean blood pressure impacted VVV's prognostic value. Altogether, an increase in VVV in SBP could signify many cardiovascular and cerebrovascular diseases field (Igase et al., 2013). Moreover, SBP variability is vital in IA formation, progression, and rupture.

GENETIC MECHANISM

A Mendelian randomization study found that genetic predisposition to higher blood pressure was associated with increased IA development risk. Their odds ratios (ORs) were 2.92 per 10 mmHg increase in diastolic blood pressure (95% confidence interval [CI]" 2.49–3.43; $P = 8.4\times10^{-40}$) and 1.87 per 10 mmHg increase in SBP (95% CI: 1.61–2.17; $P = 1.4\times10^{-16}$) (Karhunen et al., 2021).

A genome-wide association study (GWAS) exploring IA's genetic architecture found that genetic risk factors for hypertension, one main clinical risk factor, play significant roles in IA risk and drive most of the genetic correlation between IAs and other cerebrovascular traits. A cross-ancestry GWAS meta-analysis found evidence that genetic predisposition for blood pressure was independent of genetic IA causes, with an 8%–12% increase in IA risk per mmHg diastolic blood pressure increase and a 3.7%–6.0% increase in IA risk per mmHg SBP increase (Bakker et al., 2020).

Several gene expression studies have provided useful

data for interpreting hypertension's effects on IA and clarifying genetic risk factors for IA pathogenesis that could also advance our understanding of aneurysm development.

HYPERTENSION DURING THE IA RUPTURE STAGE: SIZE AND RUPTURE RISKS

There are two significant and inevitable problems with UIAs when treating them: their rupture probability and their need for prophylactic treatment. It is well known that UIA size is related to their rupture risk (Wiebers et al., 2003). Hypertension is also a component of scoring systems to predict the long-term rupture risk of UIAs (Juvela, 2022). A multicenter clinical study's multivariate logistic regression analysis suggested that rupture of small (<5 mm) UIAs was associated with hypertension (OR = 1.698, 95% CI: 1.1140–2.527; P = 0.009), with 70.4% of ruptures taking place at parent artery bifurcations, a significant independent factor (Feng et al., 2017). Recent studies showed that even smaller aneurysms (<10 mm) tend to grow (10%–15%) and possibly rupture (Bor et al., 2015). Munsterberg et al. reported a case that a patient with a newly detected small IA ruptured within 15 days and had risk factors such as smoking and hypertension (Munsterberg et al, 2021). A retrospective study showed that most aSAHs were caused by small IAs (AlMatter et al., 2019).

However, rupture risk was low for small UIAs, and hypertension was not a statistically significant predictor of rupture (P = 0.487) in a systematic review and meta-analysis of 8428 aneurysms. One potential explanation for small UIAs at different growth and stability stages is aneurysm variability with changes in the hemodynamic stress (Jiang et al., 2016). Another reason is genetic differences between races and nations (Lee et al., 2021).

A retrospective analysis suggested hypertension's significant impact on ruptured aneurysm size for SAH patients. For patients presenting with a ruptured aneurysm, the size of the ruptured aneurysm was nearly four times more likely to be <7 mm in patients with than without hypertension. Moreover, the incidence of aneurysms <7 mm was significantly higher in hypertensive patients (OR = 3.09, 95% CI: 1.95–4.92). Consequently, this study indicated that patients with risk factors such as hypertension have a lower rupture threshold and are more easily affected by hemodynamic stress (Etminan et al., 2011).

Aneurysm growth was associated with an annual rupture rate of 3.1%, while stable aneurysms had an annual rupture rate of 0.1% (P < 0.01). The annual rupture risk was >30 times higher for growing cystic IAs than for stable IAs (Brinjikji et al., 2016). These results showed that IA enlargement appears to be more important than size for rupture.

There are conflicting conclusions regarding aneurysm rupture. While aneurysm size was associated with IA rupture risk, its effect was influenced by many other factors, such as hypertension. Therefore, these observations indicate that a small UIA size, regardless of whether it is less than a threshold value, such as 7 mm, appears not to be an appropriate indicator of future UIA rupture risk (Korja & Kaprio, 2016). This limitation creates uncertainty in treating unruptured small aneurysms, especially for patients with hypertension.

RUPTURE MECHANISM IN HYPERTENSION

Consistent with their formation and development, many mechanisms are involved in IA rupture pathogenesis, including hemodynamics, inflammation, and RAS.

One study investigating hypertension's impacts on IA rupture used cessation of deoxycorticosterone acetate (DOCA)-salt treatment or taking direct vasodilator in mouse models. Captopril, an angiotensin-converting enzyme inhibitor, or losartan, an AGTR1 antagonist, was used to assess the local RAS's roles in the intracranial wall. This study found a dose-dependent relationship between reduced blood pressure and aneurysmal rupture incidence. RAS inhibition

decreased the rupture rate without influencing systemic hypertension induced by DOCA-salt treatment (Tada et al., 2014). These outcomes indicate that the local RAS in the aneurysmal wall of mouse models activated by systemic hypertension may contribute to aneurysmal rupture.

Previous reports found that gene polymorphisms in angiotensin-converting enzymes are associated with IA rupture (Slowik et al., 2004), interacting with inflammatory response and tissue reconstruction (Keramatipour et al., 2000). Therefore, the local RAS can be a therapeutic target to reduce aneurysmal rupture development (Qian et al., 2016).

Multivariable analyses found uncontrolled hypertension and RAAS inhibitor use were independently associated with the rupture risk, with the latter significantly associated with reducing rupture risk independent of blood pressure control in IA patients with hypertension (Zhong et al., 2022).

One study found that patients with aSAH used more systemic corticosteroids than controls, which their higher proportion of autoimmune diseases could explain. Corticosteroids could inhibit collagen biosynthesis in the intracranial wall, an outcome also found in IAs (Ruigrok et al., 2006). Consequently, corticosteroid use could be a risk factor for UIA rupture.

In addition to local RAS activation, systemic hypertension involves mechanical stress and the Toll-like receptor 4 (TLR4) pathway, inducing vascular inflammation and remodeling and leading to aneurysm rupture (Mitsui et al., 2020). Hypertension also leads to brain nitric oxide synthase system disorder, which involves oxidative stress, arterial injury, remodeling, and brain aneurysm formation and rupture (Fukuda et al., 2000).

Several recent studies found pulse pressure increases associated with higher C-reactive protein (CRP) and reactive oxygen species levels and adhesion molecule expression. These factors generally support the atherosclerosis-associated inflammatory process raising acute rupture risk (Hasan et al., 2015).

One study on the association between hypertension and cardiovascular disease in individuals aged 30–79 years found that the association between SBP and SAH was generally linear (hazard ratio = 1.43, 95% CI: 1.25–1·63) (Rapsomaniki et al., 2014). However, in people aged ≥60 years, SBP was no longer significantly associated with SAH.

CONCLUSIONS

Hypertension plays a significant role in IA pathogenesis. During IA formation, development, and rupture, the IA pressure varies with SBP, accelerating collagen turnover, involving inflammatory processes, and activating the local RAS. These observations have important implications for understanding how aneurysm size and blood pressure variability interact with IA under hypertensive conditions. Discrepancies among these studies show that there remain unknown mechanisms.
One crucial component in managing SAH is blood pressure management, which involves two phases. Phase 1 manages the acute hemorrhage to prevent aneurysmal re-rupture. Phase 2 aims to maintain optimal cerebral perfusion and stop delayed cerebral ischemia development, starting after the aneurysm has been secured.

One study investigating the effect of blood pressure variability on SAH outcomes showed that each mmHg pressure increase in the minimum SBP improved the likelihood of good outcomes (OR = 1.03; 95% CI: 1.001–1.064; P = 0.04) (Ascanio et al., 2020). The outcomes implied that minimum SPB might be useful in identifying at-risk patients, with a potential treatment window of 10–16 hours. In addition, this study indicated that while the optimal SBP range of 160–180 mmHg had been incorporated into guidelines, there may also be a minimum blood pressure value that can be explored.

In a clinical trial, SBP's standard deviation in the calcium-channel blockers group was lower than in the β blockers group at follow-up visits (Rothwell et al., 2010). This indicates that the effects of specific agents within individual blood pressure variability may account for discrepancies in therapeutic effectiveness. Given individual differences and genetic polymorphism, blood pressure stabilization is a potentially significant

target for therapeutic strategies with new drugs or drug combinations. In summary, further studies and clinical trials will be necessary to deepen comprehension and provide efficient management and therapies for IA patients.

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