

# Arterial stiffness and stroke: de-stiffening strategy, a therapeutic target for stroke

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## ABSTRACT

Stroke is the second leading cause of mortality and morbidity worldwide. Early intervention is of great importance in reducing disease burden. Since the conventional risk factors cannot fully account for the pathogenesis of stroke, it is extremely important to detect useful biomarkers of the vascular disorder for appropriate intervention. Arterial stiffness, a newly recognised reliable feature of arterial structure and function, is demonstrated to be associated with stroke onset and serve as an independent predictor of stroke incidence and poststroke functional outcomes. In this review article, different measurements of arterial stiffness, especially pressure wave velocity, were discussed. We explained the association between arterial stiffness and stroke occurrence by discussing the secondary haemodynamic changes. We reviewed clinical data that support the prediction role of arterial stiffness on stroke. Despite the lack of long-term randomised double-blind controlled therapeutic trials, it is high potential to reduce stroke prevalence through a significant reduction of arterial stiffness (which is called de-stiffening therapy). Pharmacological interventions or lifestyle modification that can influence blood pressure, arterial function or structure in either the short or long term are promising de-stiffening therapies. Here, we summarised different de-stiffening strategies including antihypertension drugs, antihyperlipidaemic agents, chemicals that target arterial remodelling and exercise training. Large and well-designed clinical trials on de-stiffening strategy are needed to testify the prevention effect for stroke. Novel techniques such as modern microscopic imaging and reliable animal models would facilitate the mechanistic analyses in pathophysiology, pharmacology and therapeutics.

## INTRODUCTION

Stroke is the second leading cause of death and causes excessive loss of disability-adjusted life-years every year worldwide.<sup>1</sup> Despite the reduction in stroke mortality, the absolute number of people with stroke, stroke survivors, related death as well as global burden had increased greatly in the past two decades.<sup>2</sup> In this regard, the prevention of stroke by early intervention is of great

importance. Since the conventional risk factors cannot fully account for the pathogenesis, it is essential to detect unknown stroke risk factors especially biomarker of artery injury for an appropriate intervention.

Arterial stiffness, also known as the loss of arterial elasticity, represents the mechanical property of artery resistant to deformation.<sup>3</sup> Compliance and distensibility, although related to arterial stiffness, are not interchangeable with arterial stiffness because they depend on the stiffness of arteries, as well as on the size and thickness of arteries.<sup>4</sup> Arterial stiffness has been regarded as a reliable marker of arterial structural and functional alteration after abundant experimental and clinical studies.<sup>3 5</sup> Furthermore, a growing number of studies have demonstrated the association between arterial stiffness and stroke attack.<sup>6–10</sup>

The goal of this review is to address arterial stiffness with the following aspects: the measurements, the secondary haemodynamic consequences and the predictive role, the possible pathophysiological mechanism and de-stiffening therapy for stroke prevention.

## MEASUREMENTS OF ARTERY STIFFNESS IN CLINICAL INVESTIGATION

There are various parameters to present systemic and regional arterial stiffness by different invasive or non-invasive methods. Here, we mainly discuss three major measurements of arterial stiffness that are generally applied in clinical researches.

### Assessment of pressure wave velocity

Pressure wave velocity (PWV) represents the speed of the pressure pulse travelling along the arterial region and could be obtained by automated devices, ultrasound and MRI.<sup>11</sup> On the basis of a generally accepted propagative model, the fundamental principle of mechanism is that pressure wave travels faster in stiffer artery.<sup>12</sup> Thus, PWV,

which is used to directly measure the regional stiffness, is generally accepted as the simplest, most robust, reproducible and non-invasive method of detecting arterial stiffness.<sup>13</sup> Aortic PWV is the most interesting parameter since the aorta makes the largest contribution to the buffering function and is responsible for most of the pathophysiological effects of arterial stiffness.<sup>12</sup> Therefore, the measurement of aortic PWV (mainly carotid-femoral PWV) was used in numerous clinical studies and has emerged as golden measuring criteria of arterial stiffness in adults.<sup>13</sup> The 2013 European guidelines for the management of hypertension and cardiovascular disease prevention in clinical practice even recommended that aortic PWV be used to assess target organ damage.<sup>14</sup> The limitations of PWV measurement should be mentioned here. It remains difficult to accurately record the femoral pressure wave in participants with peripheral artery disease, and obesity effects the absolute value of PWV by overestimating the distance.<sup>13</sup>

Cardio-ankle vascular index (CAVI), one of the PWV measurement modifications and derived from arterial stiffness index  $\beta$ , was introduced by Japanese experts to obtain arterial stiffness not affected by blood pressure (BP) at a measuring time; thus permits for the first time to analyse the effect of antihypertension drugs on arterial property.<sup>15</sup> CAVI exhibited reproducibility among various vascular diseases.<sup>10, 16</sup> However, the limitations of CAVI should also be concerned. CAVI cannot be measured accurately in patients with aortic stenosis, peripheral arterial disease or atrial fibrillation.<sup>17</sup> CAVI usually evaluates the vascular condition of large arteries.<sup>18</sup> In addition, the mixture of functional and anatomical concept also limits its clinical application.

### Analysis of the arterial pressure waveforms

Pulse wave can be analysed through three major parameters: augmentation index (AIx), pulse pressure (PP) and systolic BP. Wave reflection occurs at sites of impedance mismatch and is quantified by the AIx, calculated as the difference between the second and the first systolic peaks expressed as a percentage of the PP ( $AIx = \Delta P / PP$ ). AIx is usually obtained from carotid, ascending aortic or radial artery waveforms recorded by applanation tonometry. AIx may be incorrectly assessed due to the technical difficulty in identifying the return time of the reflected pressure wave and the fiducial point.<sup>19</sup> In addition to the amplitude of the reflection wave, AIx is also determined by the distance to the reflected site, PWV as well as cardiac cycle. Therefore, it is an indirect measurement of arterial stiffness and should be analysed in combination with PWV. From a clinical point of view, AIx is often used to evaluate the effect of de-stiffening drugs on wave reflection.<sup>13</sup> As an innovative method, AIx has not yet been validated in large prospective clinical trials.

Central PP and systolic BP are the crude indexes of large artery stiffness, and present as more powerful indicators for the cardiovascular events than periphery ones.<sup>20</sup>

While there is no non-invasive technique available to directly measure central PP, the most widely used approach is to measure the brachial PP by a sphygmomanometer and then apply the transfer function. However, the premise of using the transfer function is that the characteristics of the vascular system between the two measuring sites are the same in all individuals and under all conditions. Apparently, this is not true since vascular dimension depends on body size, and vascular properties vary with arterial pressure, with age and with treatment.

### Measurement of arterial diameter change with respect to the distending pressure

Unlike PWV, which is the measurement of regional arterial stiffness in a certain segment, the measurement of changes in arterial diameter and volume can help evaluate the elasticity of the local artery. Echo tracking system or MRI is performed to acquire local stiffness index like compliance, distensibility, Young's elastic modulus and incremental elastic modulus. Compliance is defined as the change in arterial volume relative to change in pressure while distensibility is analogous to compliance but after normalisation of arterial size. The curvilinear relationship between pressure and diameter is approximated with a logarithmic transformation, resulting in the  $\beta$  index reflecting the stiffness.

However, the pressure–diameter or pressure–volume relations depend both on the stiffness of the vessel wall and on the vessel geometry including artery size and wall thickness.<sup>21</sup> Besides, it requires a high degree of technical expertise and takes longer than measuring PWV. This method is applied more in mechanistic analyses than in epidemiological studies.<sup>13</sup>

### MECHANISM OF ARTERIAL STIFFNESS

Vascular structure, vascular function and BP are the three major components that are involved in arterial stiffness. Factors such as inflammation, oxidative stress, the renin-angiotensin-aldosterone system (RAAS) and genetic factors that influence the function of vascular in short term or the structure in long term can induce arterial stiffness.<sup>22, 23</sup>

#### Vascular structure

Vascular structure is a major determinant of arterial stiffness. When stiffened vessels were examined microscopically, the change in the property or the distribution could be observed including increased collagen and matrix metalloproteinases (MMPs), fragmented and diminished elastin, abnormal and disorganised endothelium, infiltration of smooth muscle cells, macrophages and mononuclear cells.<sup>3</sup>

*Extracellular matrix remodelling:* Scaffolding protein collagen and elastin are closely linked to the strength and elasticity of the vessel. Normally, MMPs play a vital role in regulating the synthesis and degradation of these two proteins. Inflammation, haemodynamic or genetic

factors could break the synthesis/degradation balance and raise the ratio of collagen/elastin, thus increasing arterial stiffness.<sup>24</sup>

Cross-links between collagen and elastin in the arterial wall are significant in providing elasticity and strength to the arteries. Owing to the glycation of proteins, especially collagen, advanced glycation end products (AGEs) are formed, which create excessive cross-links between collagen and consequently induce arterial stiffness.<sup>25</sup> AGEs could also influence the stiffness of the artery wall by the receptor-mediated endothelial dysfunction and inflammation process. From a prospective study conducted in patients with early rheumatoid arthritis, arterial stiffness was improved greatly after 12-month treatment of anti-inflammation.<sup>26</sup>

*Smooth muscle cell hypertrophy:* Alteration in mechanical aortic wall properties accompany with reduction in compliance and distensibility preceded the development of hypertension in spontaneously hypertensive rats.<sup>27</sup> While there was no significant difference in collagen content between young spontaneously hypertensive rats and normotensive rats, the media thickness and cross-sectional area were significantly larger in hypertensive rats. Vascular smooth muscle cell hypertrophy, which is mainly responsible for media thickness, participated in the development of arterial stiffness.

### Vascular function

*Endothelial dysfunction:* Endothelial dysfunction embodies its indispensable role in vascular disease by releasing vasoactive substances. Nitric oxide (NO) has a vasodilatory effect and exhibits antiatherogenic property through inhibition of vascular smooth muscle cell proliferation.<sup>28</sup> Blocking endothelium-derived NO synthesis resulted in higher arterial stiffness.<sup>29</sup> Impaired endothelial function was independently and inversely related to PWV, AIx and central PP as shown in the large-scale study among healthy participants.<sup>5</sup> In fact, there might exist a vicious circle between endothelial dysfunction and arterial stiffness, that is, endothelial dysfunction could aggravate structural stiffening and, in turn, worsen endothelial function.<sup>24</sup>

*Smooth muscle tone:* Smooth muscle tone modulates the artery elasticity. Vasodilators decrease the smooth muscle tone, cause a reduction of wave reflection and raise the distensibility.<sup>30</sup> Vasoconstrictors such as angiotensin II, on the other hand, lead to loss of elasticity in the vessel wall.<sup>31</sup> The endothelial dysfunction interacts with impaired muscle tone via these released vasoactive substances in the progression of elasticity alteration.

### Blood pressure

Arterial stiffness depends on cyclic strain of the arterial wall, mainly the cyclic change of BP. At a low BP level, the elastin controls the composite behaviour and the vessel wall is relatively extensible, while at a high BP level, the collagen with stiffer property is increasingly important and then the vessel wall becomes

inextensible.<sup>21–32</sup> Therefore, arterial stiffness increases at a higher BP even without structural change.

### HAEMODYNAMIC PATHOGENESIS SECONDARY TO ARTERIAL STIFFNESS

Among the various models that applied to the circulatory system for a better understanding of haemodynamics, the propagative model based on a viscoelastic tube hypothesis is the most acceptable one.<sup>12</sup> In this model, the elastic properties of the tube allow the generation of a forward pressure wave, which travels along the tubes. On the other hand, the numerous branch points and high resistance of the tubal end favour the wave reflection and generate retrograde waves. In healthy participants, reflected waves arrive at the central aorta during the diastole phase, contributing to the secondary fluctuation of the pressure waveform, which benefits the coronary perfusion.

With increased arterial stiffness, the forward and reflected wave travel more rapidly along the arterial tree, leading to an earlier arrive in late phase of systole. Therefore, the reflected wave amplifies systolic BP and PP, increases the after load and may lead to ventricle hypertrophy in the long run. A raised PP damages small arteries in peripheral organs, thus in turn inducing arterial stiffness.

Increased arterial stiffness could also promote excessive flow pulsatility into small vascular beds. Unlike most vascular beds which are protected by intense vasoconstriction upstream, the brain is more susceptible to pressure and flow pulsatility.<sup>33–34</sup> This haemodynamic stress, pulsatile pressure or BP variability can cause a 'tsunami effect' towards cerebral parenchyma.<sup>35</sup> This might help explain how aortic stiffness damages microvasculature and causes dysfunction.<sup>36–37</sup>

### ARTERIAL STIFFNESS: A PREDICTOR OF STROKE

An indirect clue for the influence of arterial stiffness on stroke comes from early cross-sectional studies. Patients with cardiovascular risk factors or vascular diseases such as coronary heart disease and end-stage renal disease had higher arterial stiffness than did the control group.<sup>38–39</sup> The first study on arterial stiffness in patients with stroke evaluated vascular stiffness by calculating index  $\beta$ . Index  $\beta$  was significantly greater in patients with stroke than in the control group, indicating that aortic stiffness was independently associated with ischaemic stroke.<sup>40</sup> Later, more and more large case-control studies confirmed that greater arterial stiffness was common in patients with stroke.<sup>41–42</sup> Owing to the cross-sectional nature of these studies, it was impossible to conclude that vascular stiffness was predictive of stroke.

Later longitudinal studies demonstrated that vascular stiffness was an independent predictor of cardiovascular and all-cause mortality in patients with hypertension, early-stage renal disease and in the elderly population.<sup>43–45</sup> However, stroke was only discussed as one of the clinical end points until Laurent *et al*<sup>46</sup> first

investigated the association of vascular stiffness and fatal stroke occurrence in a cohort survey. After an average 7.9 years follow-up of middle-aged patients with essential hypertension, Laurent *et al* found that a 1-SD elevation (4 cm/s) in PWV was associated with a 72% higher risk of fatal stroke. High PWV remained significantly predictive of stroke death after adjustment for classical cardiovascular risk factors. Other researchers assessed its predictive value in the elderly and general population.<sup>6 47</sup> Data from two recent meta-analyses suggest that the assessment of aortic or carotid stiffness could both improve the prediction of stroke beyond other conventional risk factors.<sup>48 49</sup> In addition, aortic stiffness could predict the prognosis of ischaemic stroke.<sup>7 50</sup> Carotid-femoral PWV measured 1 week after stroke was significantly associated with a 90-day functional outcome valued by the modified Rank Scale in patients.<sup>7</sup>

As to different subtypes of stroke, vascular stiffness seems to have different predictive value.<sup>8 9 51</sup> Stroke is a heterogeneous disease due to its varied pathophysiology in each subtype. Patients with lacunar stroke tended to have a higher PWV compared with large artery atherosclerosis, cardioembolic and cryptogenic stroke.<sup>51</sup> Increased arterial stiffness with greater flow pulsatility into a cerebral small vessel may contribute to the pathogenesis of lacunar stroke, thus resulting in the difference. Another study demonstrated that aortic stiffness index  $\beta$  was higher in patients with cerebral infarction than in those with a transient ischaemic attack, implying that cerebral infarction is associated with a more advanced degree of atherosclerotic process than transient ischaemic attack.<sup>9</sup> Larger studies that evaluate the relationship between vascular stiffness and each subtype stroke are imperative to help clarify the direct interaction in pathogenesis and provide specific insights into efficient stroke prevention.

In recent years, high resolution MRI provides a unique tool to study the relationship between vascular stiffness and neuroimaging changes relevant to the recurrence or severity of stroke. Cerebral small vessel disease (SVD), which can increase the risk of stroke, is linked to arterial stiffness.<sup>35 36 52 53</sup> A study of 1282 patients with acute ischaemic stroke or transient ischaemic attack showed that brachial-ankle PWV was significantly associated with both acute and chronic cerebral SVD markers including acute lacunar infarct, chronic lacunar, white matter hyperintensity, deep cerebral microbleeding.<sup>52</sup> In the general elderly population of the Rotterdam scan study, higher PWV was also related to larger white matter lesion volume, but not to lacunar infarcts or microbleeding.<sup>53</sup> Vascular stiffness and cerebral SVD could share a common pathophysiological mechanism involving vascular injury.

## MECHANISM OF ARTERIAL STIFFNESS DURING STROKE

A variety of mechanisms could interpret the association between arterial stiffness and stroke. Haemodynamic

alterations secondary to arterial stiffness should be highlighted. Raised PP induces arterial remodelling, increases wall thickness, promotes the development of plaque and atherosclerosis, and eventually lead to rupture or ulceration of atherosclerotic plaques. Besides, increased aortic pulsatility may also transmit through stiffen large vessels to the cerebral microvasculature. As the central artery stiffen, the capacity to regulate the pulsatile flow is reduced, which leads to progressive impedance matching between the aorta and peripheral arteries. Such impedance cause a decrease in the reflection coefficient and thereby facilitates the penetration of excessive pulsatile energy into the periphery.<sup>54</sup> To make it worse, the vascular resistance of the brain is relatively low; therefore, the pulsatility of pressure and flow extend well into this organ. This special input impedance of the brain provides an interpretation for how arterial stiffness damages the cerebral microvasculature and causes impaired cognition function.<sup>33 51 54</sup>

Furthermore, the measured higher aortic stiffness may reflect parallel structural changes in the intracerebral vasculature, including elastic fibres broken down, fibrosis, calcifications, medial smooth muscle necrosis and diffusion of macromolecules into the arterial wall.<sup>55</sup> Finally, the classical vascular risk factors or vascular diseases such as hypertension, atherosclerosis, coronary heart disease and early-stage renal disease, which are associated with and even probably promoted by arterial stiffness, are also risk factors for ischaemic stroke.

## THE DE-STIFFENING THERAPY AND STROKE PREVENTION

It has aroused enormous interest whether the reduction on arterial stiffness can translate into real clinical benefits on stroke management. De-stiffening therapy emerges as a promising strategy to decrease stroke incidence or mortality and improve functional prognosis. On the basis of numerous clinical trials, antihypertension drugs are successful at reducing BP and stiffness.<sup>56–58</sup> However, it is difficult to separate the effect of intervention on BP reduction alone from their direct effect on the property of the vessel wall. It is of utmost importance to break the vicious circle between arterial stiffness and raised PP. Targeting structural factors in vascular signalling remains largely unexplored, yet progression should not be ignored. Exercise training is another effective non-pharmacological method in attenuating arterial stiffness.

## Pharmacological interventions

**Antihypertension drugs:** The most important mechanism of antihypertension drugs improving arterial stiffness is the efficacy in lowering BP.<sup>59</sup> For the same BP reduction, antihypertension drugs which improve arterial stiffness to the greatest extent should be privileged. The BP-independent effect comes from the alteration on arterial function, structure or a combination of both. Antihypertension drugs with vasodilation activity such as

ACE inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB) and some  $\beta$ -block (BB) have shown advantage in ameliorating arterial stiffness.<sup>60–61</sup> Most of the de-stiffening strategy preferred the administration of RAAS inhibitors combined with a CCB or a diuretic.<sup>59</sup>

**ACEI/ARB:** Among all classes of the antihypertension drugs, the RAAS inhibitors are generally recognised to be superior to others in reducing arterial stiffness.<sup>56–62–63</sup> The most probable explanation lies in the profibrotic action of the RAAS. Owing to the antifibrotic potency of RAAS inhibitors, the extracellular matrix in the vascular wall is reversed, which finally translates into a change in mechanical property of the vessel.<sup>64</sup> In addition, ACEI could modulate endothelial function via releasing bradykinin and NO.<sup>65–66</sup> Numerous studies including both long-term ones (such as the REASON trial, the ADVANCE trial) and short-term to medium-term ones showed a reduction of arterial stiffness when ACEI or ARB was used.<sup>67–69</sup> When comparing ARB to ACEI, taking valsartan and captopril, for example, could equally reduce PWV as well as AIx.<sup>70</sup> A combination of ACEI and ARB proved to achieve an even greater effect on PWV reduction in patients with chronic kidney disease.<sup>71</sup> Clinical trials also confirmed the efficacy of RAAS inhibitors in improving patient survival and reducing cardiovascular events.<sup>72–73</sup> The PROGRESS trial (n=6105) demonstrated that after a 4-year follow-up, the ACEI regime reduced the risk of recurrent stroke by 28% among participants with previous stroke or transient ischaemic attack.<sup>72</sup>

**CCB:** CCB also proved to lower PWV and AIx, but to a lesser extent than RAAS inhibitors did.<sup>57–74–75</sup> The largest amount of evidence came from trials evaluating amlodipine.<sup>57–76</sup> A combination of CCB and ARB had an advantage over the combination of diuretics and ARB for less side effects and more arterial stiffness improvement.<sup>74–75</sup>

**Diuretic:** Although the combination of diuretics and ACEI/ARB has been merged as one of the most common regimes in treating hypertension, the role of diuretics on treating arterial stiffness has not been well explored.<sup>58–77</sup> A 4-week study demonstrated that hydrochlorothiazide failed to decrease PWV and AIx in spite of a reduction in brachial BP, which imply no favourable effect of diuretics on arterial stiffness beyond BP reduction.<sup>76</sup>

**BB:** BB is less valuable in reducing arterial stiffness, probably because it reduces BP by lowering the cardiac output, which instead increases periphery resistance and the wave reflection. BB is far beyond homogeneous, and the effect of arterial stiffness by BB could be either favourable or unfavourable. A recent meta-analysis reported that BB increased AIx, whereas all other antihypertension drugs decreased AIx.<sup>78</sup> Furthermore, another meta-analysis from 13 randomised controlled trials suggested that BB is inferior to prevent stroke by reporting that the relative risk of stroke was 16% higher by BB than other kinds of antihypertension drugs.<sup>79</sup> Novel BBs

with vasodilation activity such as nebivolol and carvedilol display the ability to decrease arterial stiffness, but need to be further investigated with large-scale prospective trials.<sup>80–81</sup>

**Antihyperlipidaemic agents:** The data on statins are somewhat conflicting.<sup>82–83</sup> A systemic review of nine trials with 471 participants disproved the effect of statins on reducing arterial stiffness, but this conclusion might relate to the methodological limitation that the included trials only studied aortic or peripheral elasticity at a time.<sup>82</sup> A recent clinical study, which was designed to measure both aortic PWV and AIx at the end of a 26-week follow-up, supported the role of statins in ameliorating stiffness through anti-inflammatory and antiproliferative properties.<sup>83</sup> The percentage reduction in PWV by fluvastatin was associated with that of serum C reactive protein independent of the lipid-lowering effect.<sup>84</sup>

**Other drugs:** Other drugs that target vascular signalling in arterial stiffness development have achieved some progression. MMP inhibitors include endogenous tissue inhibitors and pharmacological inhibitors such as zinc chelators, doxycycline and marimastat, of which only doxycycline is approved by the Food and Drug Administration (FDA).<sup>85</sup> In two-kidney one clip hypertensive rats, doxycycline (30 mg/kg per day, 4 weeks) successfully prevented surgery-induced increases in systolic BP and MMP-2 levels, reduction in endothelium-dependent vasodilation and vascular hypertrophy.<sup>86</sup> However, in spontaneously hypertensive rats, though structural alteration was ameliorated after 6 months treatment of doxycycline, arterial pressure, PWV and left ventricular function were unaffected.<sup>87</sup> The efficacy of doxycycline and other MMP inhibitors in reducing arterial stiffness needs to be studied by different measurements and in different animal models.

AGEI which can prevent AGE cross-linking and AGE breaker which can break the AGE cross-links were found to attenuate arterial stiffness by interfering the arterial remodelling in animal experiments.<sup>88–89</sup> Alagebrium chloride (also known as ALT-711), a novel non-enzymatic breaker of AGE, reduced AIx in patients with isolated systolic hypertension and such effect was related to improved endothelial function.<sup>90</sup> However, the study enrolled only 13 patients and the therapy lasted for only 8 weeks. Later, in a randomised trial, a 1-year administration of ALT-711 failed to affect arterial stiffness or endothelial function.<sup>91</sup> Despite the promising effect in reversing ventricular stiffness, the efficacy of AGEIs and AGE breakers in alleviating arterial stiffness needs long-term and high qualified research.<sup>92</sup>

### Exercise training

Arterial stiffness increasing with ageing was less pronounced in physically active men and women.<sup>93–94</sup> Several studies have shown the efficacy of aerobic exercise in preventing age-related arterial stiffness in healthy individuals and reversing arterial stiffness in patients with vascular risk factors as well.<sup>95–97</sup> Aerobic exercise

could also induce improvement in cardiovascular haemodynamics including arterial stiffness after stroke.<sup>98</sup> The mechanism by which aerobic exercise improves arterial stiffness remains little known and is considered relevant to the raised NO availability and lowered oxidative stress.<sup>99</sup> Physical activity could also modify gene polymorphisms that determine stiffness.<sup>100</sup>

The intensity, duration and frequency of aerobic exercise required for attenuating arterial stiffness is unclear. It has been recently established that 8 weeks of intermittent moderate aerobic exercise reduced stiffness parameters significantly in young healthy volunteers.<sup>95</sup> A recent systematic review concluded that the effect of aerobic exercise improving arterial stiffness was enhanced with higher intensity.<sup>101</sup> The improvement in arterial stiffness following aerobic exercise is also influenced by participants' features. When it came to the elderly with multiple cardiovascular risk factors, though there was a decrease in arterial stiffness after 3-month training, the effect was not sustained after 6 months.<sup>102</sup> Resistance exercise has an inconsistent effect on arterial stiffness.<sup>103 104</sup> A meta-analysis demonstrated that high-intensity resistance training seemed associated with an 11.6% increase in stiffness while moderate-intensity resistance training did not show such association.<sup>104</sup> In conclusion, larger reproducible clinical trials are needed to set the appropriate training type and pattern for specific groups.

In summary, arterial stiffness, which can reflect the characteristic of arterial structure and function, is a novel and reliable predictor of stroke and offers a promising strategy to intervene stroke.

## PERSPECTIVES

Large and well-designed clinical trials on de-stiffening strategy are needed to further testify the prevention effect for stroke. Besides, development of reliable animal models and novel invasive techniques are extremely important to reveal the role of vascular stiffness in the progression of cerebrovascular disease. Hopefully, a recently developed animal model that is based on carotid calcification claims to meet all the characteristics of arterial stiffness without any unspecific effects such as brain hypoperfusion.<sup>105</sup> The newly advanced techniques such as synchrotron radiation angiography may provide a new tool to observe the secondary flow pulsatility into brain vascular bed and help understand the contribution of arterial stiffness to cerebral microvasculature damage.<sup>106</sup> This might fill gaps in understanding the pathophysiology involved in how arterial stiffness contributes to ischaemic stroke and offers theory foundation for therapeutic intervention.

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