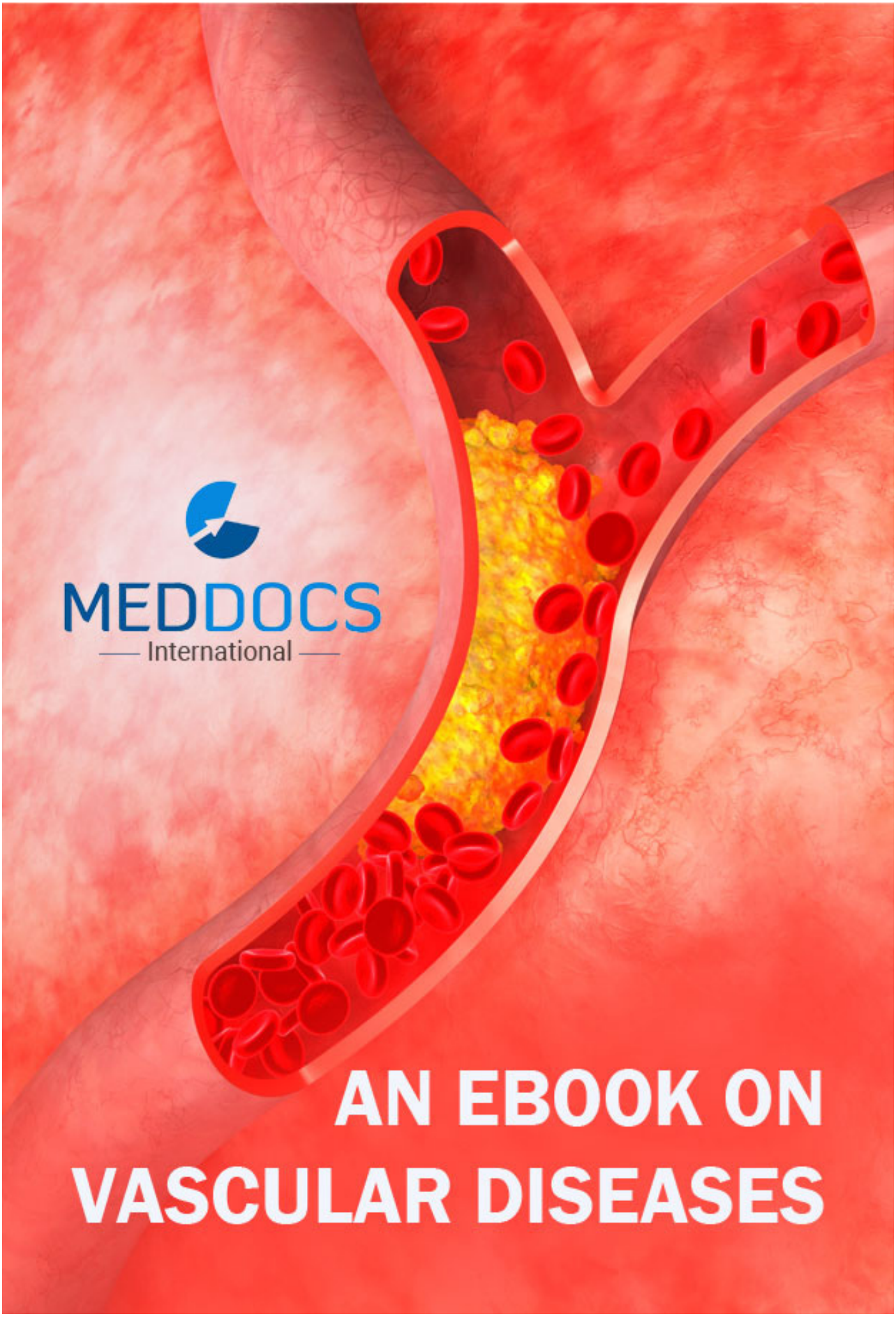

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Arterial de-stiffing Drugs: Which Promising Therapeutic Agent is Useful?

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Abstract

Degeneration of medial layer of elastic arteries with deposition of collagen is termed arterial stiffness, and considered as a risk factor of cardiovascular events. Several mechanisms are involved in the pathogenesis of arterial stiffness, and there are a lot of diseases that associated with arterial stiffness. Drugs that reverse the arterial stiffness should be producing their effect on the medial layer independent on their effects on the blood pressure, and other risk factor. Moreover, their effects should be sustainable without producing harmful adverse reactions. This review discusses the property of each class of drugs that showed destiffness effect.

Introduction

Overview

Arterial Stiffness (AS) is degeneration of the extracellular matrix in the medial layer of the elastic arteries which characterized by a crosslinking of the elastin fatigue-fracture and deposition of the collagen. It occurs mainly in the proximal rather than distal arteries [1]. It is usually diagnosed by demonstrating an increase of the Pulse Wave Velocity (PWV) on one side of the target organ and a stiffness gradient on the other side between the proximal and distal arteries. Therefore, AS impaired the microcirculation of the target organ, including the heart, and the PWV is used as a predictor of cardio-vascular event, as an increase of 1m/s of PWV value contributes to an increase of 14% of Cardiovascular (CV) events [2].

Measurements of arterial stiffness

Measurement of the PWV is the most common technique that evaluate the stiffness of the peripheral arteries [3]. It can be measured on any artery or in between arteries area. Carotid-Femoral Pulse Wave Velocity (cfPWV) measurement is the most reliable test of assessment the AS, with a cutoff value of 10m/s [4-6]. Determination of arterial stiffness can be achieved by measuring the WPV at Carotid-Radial (crPWV), Femoral-Tibial (ftPWV), Brachial-Ankle (baPWV), or even use single-point PWV measurement [7]. Augmentation Index (AI) is a simple measurement which calculated by using the formula; (augmentation pressure/pulse pressure) X 100, where the augmentation pressure is the wave reflection from peripheral vessel to the central vessel (aorta). It is considered as an indirect measurement of AS, and it significantly increases with age [8]. The other measurement of AS is determination of Cardio-Ankle Vascular Index (CAVI). This diagnostic tool is based on the determination of the distensibility of carotid artery i.e. β-stiffness to the all arterial segments between the heart and ankle using PWV. The advantage of this diagnostic tool is independent to the blood pressure level, and it can carried at any time [9].

There are many circulating biomarkers that linked to AS and their measurements can aid in diagnosis as well as prognosis of AS. Among these biomarkers, are:

Transforming growth factor-β1 (TGF-β1)

Although this factor is increased in alcoholic patients with coronary artery disease, and it strongly correlated with low density lipoprotein, but it is not correlated with brachial-ankle index or calcification of aortic arch [10]. This means that TGF-1β is not a useful determinant of AS.

Fibroblast growth factor 21 (FGF21)

This factor is an independent factor that determines cfPWV in Type2 Diabetes (T2D) with a cutoff value of 184pg/ml [11]. FGF21 correlates with cfPWV, independently to the age and it can consider as a biomarker of predicting subclinical atherosclerosis.

Soluble ST2

It is a biomarker of myocardial fibrosis and remodeling. This marker is elevated in patients with heart failure and coronary heart disease [12,13]. Kim et al (2019) reported that patients with coronary artery stenosis have significant high levels of aortic pulse pressure and the circulating sST2 which are strongly correlated [14].

Endocan

It also named as endothelial cell specific molecule1. It is a specific inflammatory marker of CV events [15]. Serum level of endocan is increased in patients with a newly diagnosed essential hypertension, and its level is correlated with aortic distensibility, aortic strain, but it does not correlate with aortic stiffness index [16].

Adipocytokines

In young healthy subjects, there is a non-significant correlation between serum leptin and the aortic PWV (aPWV) despite the value of the body mass index [17]. On the other hand, a significant high serum level of leptin is significantly correlated with a higher value of cfPWV in patients with coronary artery disease. Odd ratio extracted from the multivariable regression analysis was 1.026 for leptin after adjusting other risk factors [18]. In non-alcoholic fatty liver disease, there is no correlation between AS(assessed by brachial to ankle PWV; baPWV) with the adiponectin-to-leptin ratio [19]. Low serum level adiponectin is an independent risk factor of aortic stiffness in T2D and hypertension, and significant correlations between afWPV (at aortic femoral segment, and baPWV with the serum level of adiponectin were observed [20, 21].

Cystatin C

In general population study included 748 subjects, the aPWVis significantly correlated with systolic blood pressure, body mass index, and serum lipid profile and cystatin C levels [22]. This observation highlights the role of inflammation in predisposing the AS there is no study carried carried on the general population with normal renal function.

Fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c)

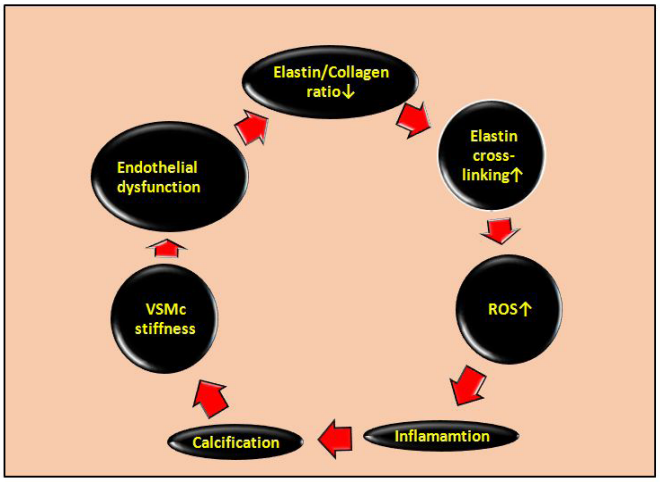
A significant high value of baPWV was observed in patients with combined pathology of hypertension and diabetes. Also, significant correlations between PWV with glycemic indices (strongly correlated with HbA1c) regardless of the diabetes status, were observed [23]. FPG and HbA1c are strong predictors of developing AS in in black African men, which independent to other confounding factors [24]. Therefore, HbA1c is considered as an early marker that predicts AS.

Risk factors associated with arterial stiffness

Arterial stiffness is associated or complicated by many disorders and syndromes **(Table 1).** In addition, there are many risk factors that shared in inducing AS through different mechanisms **(Figure 1)**.

Table 1: Conditions associated with arterial stiffness

Hypertension	Chronic kidney disease	Chronic obstructive lung disease	Ankylosing spondylitis
Pulmonary hypertension	Nephrotic syndrome	Cystic fibrosis	Systemic lupus erythematous
Peripheral arterial disease	Polycystic kidney disease	Sarcoidosis	Rheumatoid arthritis
Congenital heart disease	Renal stones		Polymyalgia rheumatica
Coronary artery disease	Polycystic ovary syndrome	Hereditary hemolytic anemia	Vasculitis
Stroke		Primary thrombocythemia	
migraine	Non-alcoholic and alcoholic fatty liver disease	Hematological malignancies	Human Immune-deficiency Virus infection
			Septicemia
Diabetes mellitus	Liver cirrhosis	Phenylketonuria	Organ transplantation
Metabolic syndrome	Chronic hepatitis	Marfan's Syndrome	Drug abuse
Thyroid gland disorders	Gall stones	Congenital adrenal hyperplasia	
Parathyroid glands disorders	Inflammatory bowel disease		
Adrenal gland disorders			
Acromegaly			



ROS: Reactive Oxygen Species; VSMc: Vascular Smooth Muscle Cell

Figure 1: Mechanisms of arterial stiffness at the cellular level.

Risk factors of arterial stiffness included

Ageing

The elasticity of the blood vessels declined with ageing due to the replacement of the elastin fibers with the collagen fibers within the wall of the blood vessels. Women are less likely to have AS compared with men irrespective to the risk factors [25]. There is a link between ageing process and inflammation which facilitates the occurrence of AS. Healthy subjects aged >40 years, have significant higher serum levels of IL-6, TNF-α, and the complement (C1q) as well as cfPWV compared with subjects aged <40 years [26]. The complement C1q is increasing from the age of 30 years, and it is strongly correlates with PWV after adjusting other confounding factors [26].

Genetic

It is demonstrated in many hereditary diseases. Patients with classical Phenylketonuria have a significant high mean value of aortic PWV (6.6 m/s) compared with health subject (5.26m/s) [27]. Variation of apolipoprotein A5 gene (including rs662799 and rs2075291) is associated with low serum level of high density lipoprotein, low serum adiponectin level, and high value of baPWV [28]. Black African people complained from uncontrolled blood pressure and AS, which partly due to abnormal increased activity of epithelial sodium channels (ENaC) due to genetic variation of ENaC [29]. Wnt genes (APC, TCF) expression was found among 14-related genes in elderly healthy African men presented with a significant high ba PWV values, indicating the role of Wnt pathway in the development of AS [30].

Smoking

Smoking is an important risk factor that caused AS and associated with peripheral artery disease. Current smokers have a significant high radial AI compared with non-smokers. Ex-smokers usually did not show a significant increase of radial AI at a cutoff value of smoking-quit duration >1 year [31]. Other studies demonstrated that smoking cessation for 3 years improved the AI which dependent on the reducing blood pressure [32]. Young age people (aged 17 years old) who smoked cigarette >100 in their life had significant high values of cfPWV compared with non-smokers, and those who quit smoking had a mean value of cfPWV similar to the non-smokers [33].

Alcohol

Charakida et al (2019) reported that young age subjects drunk more than 10 drinks per day had a significant high value of cfPWV (5.85 ± 0.8 m/s) compared with people drinking < 2 drinks per day (5.67 ± 0.604 m/s) [33]. In another cross-sectional study carried on Chinese people, alcohol drinking was not significantly influence the crPWV, indicating that alcohol did not involve in the pathogenesis of peripheral artery diseases [34].

Betel nut chewing

The prevalence of arterial stiffness (ba PWV≥1.4m/s) among ex-and current betel nut chewers are 42.3% and 43.2% after adjusting other cofounder factors [35]. This observation indicates that the effect of betel nut on the blood vessels is irreversible compared with tobacco users or alcohol drinkers.

Metabolic syndrome components

Metabolic syndrome is a strong risk factor of AS. Hypertension, diabetes mellitus, obesity and dyslipidemia are components of metabolic syndrome and they cause AS and CV events. Hypertensive non-diabetic patients with evidence of metabolic syndrome had a significant high aPWV (10.0±2.7m/s) compared with participants without metabolic syndrome (8.8±2.1 m/s). Moreover, aPWV correlated positively and significantly with blood pressure, waist circumference and non-significantly with body mass index [36]. Moreover, normotensive patients with metabolic syndrome also have a significant PWV compared with participants without metabolic syndrome [37]. This observation indicates that more than one risk factors shared in inducing AS. Obesity is a risk factor of development of AS. The relationship between obesity and AS is little pit complex. Impedance body composition analyzer (an investigational tool that can determine the body mass index; waist circumference; and body fat percentage) is used clinically in assessment of AS. Arterial distensibility rather than Young's elastic modulus and β stiffness index, as markers of local stiffness of the carotid artery, is strongly associated with body composition in both sexes [25].A significant positive correlation between the body mass index and baPWV is found but at the same time obese people have a mean value of baPWV (445.2 ± 245.2 cm/s) less than corresponding value of over-weight people (1490 ± 308 cm/s) after adjusting all risk factors [38]. In adolescent, central obesity shared other components of metabolic syndrome (i.e. dyslipidemia, high blood pressure, and glucose intolerance) are risks factors of significant increase of baPWV [39]. Pathological arterial stiffness simple resolve after bariatric surgery as aa mean value of PWV is decreased from 10.1 m/s (before surgery) to 7.5m/s (after3 months of surgery) [40]. Perivascular adipose tissue significantly increased with ageing, and correlated with AS. This observation explained by demonstration different factors that derived from perivascular adipose tissue and played a role on the signaling regulation of the vascular tone, local inflammation and remodeling of the blood vessel structures [41].

Dyslipidemia, in term of high serum triglyceride and low density lipoprotein and low serum level of high density lipoprotein, is a known risk factor of developing AS. Recent study focuses on the using Nuclear Magnetic Resonance to assess the lipid profile in patients had AS. It has been found that aPWV in healthy subjects associated with low density lipoprotein subclass, while in Type-1 Diabetes (T1D) is associated with very low density lipoprotein [42]. In hypertensive patients with or without dyslipidemia, AS (determined by baPWV) is correlated with total cholesterol, high density lipoprotein, atherogenic index of plasma, and the ratio of triglyceride-to-high density lipoprotein

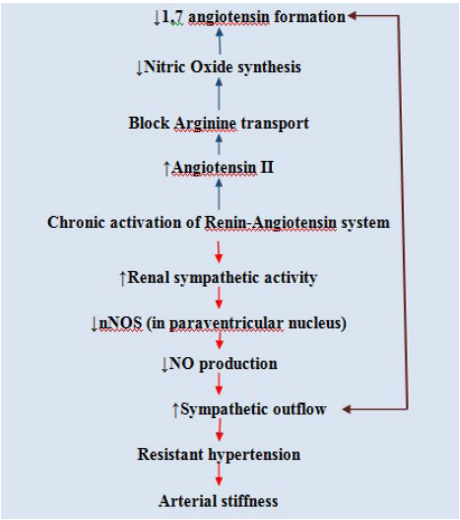
but not to triglyceride, or high density lipoprotein or non-high density lipoprotein [43].

Inflammation

Local inflammation is usually accompanied by liberation of the cytokines which impair the relaxation of the vascular smooth muscle relaxation through reducing the bioavailability of NO and generation of endothelin-1 [44]. Chronic inflammation causes extracellular matrix stiffness and calcification leading to loss of the elastin [44]. In healthy subjects aged >40 years, the serum levels of IL-6, TNF-α, and C1q as well as cfPWV were significantly increased compared with subjects aged <40 years. The complement C1q started increasing from the age of 30 years, and it is strongly correlated with C1q after adjusting other confounding factors [26]. In young onset hypertension, serum levels of inflammatory cytokine including IL-6 and MCP-1 are significantly increased with a parallel increment of cfPWV despite there is no significant difference in the intima-media thickness between patients and controls [45]. Although inflammation is considered in the pathogenesis of AS, there is evidence, based on the population study included 447 subjects, that patients consumed non-steroidal anti-inflammatory drugs are significantly have aortic stiffness compared with others ingested other drugs [46].

Oxidative and nitrative stress

Oxidative and nitrative free radicals that generated from conditions that inducing or associating with risk of cardiovascular events, are participated in the AS. Therefore, these radicals played a role in endothelial dysfunction due to the arterial fibrosis and stiffness thorough their effects on the endothelial cellular elements including enzymes, lipid, and DNA [47]. Therefore, nutraceutical or pharmaceutical medicines having antioxidant properties are useful in management of AS e.g. curcumin, wine, metformin, sartans, etc. An increase of cfPWV is significantly correlated with the peroxide level [48]. In one clinical study carried on subjects fed with high fat diet to induce hypercholesterolemia, the serum level of 3-nitrotyrosine (a marker of nitrative stress) is significantly correlated with aPWV [49]. In addition there is an interaction between generation of NO (which is a powerful vasodilator neurotransmitter), angiotensin II (a power vasoconstrictor) and the activation of sympathetic autonomic nervous system, which induced arterial stiffness **(Figure 2)**.



nNOS: neuronal Nitric Oxide Synthase; NO: Nitric Oxide

Figure 2: The role of nitric oxide, angiotensin II and sympathetic outflow in precipitating arterial stiffness.

Pharmacological interventions in the management of arterial stiffness

Non-pharmacological interventions are useful in controlling the AS like exercise, low salt diet and controlling of the other modifiable risk factors. This review concerns with the pharmacological intervention. Therefore, there are many pharmacological modalities can impact a beneficial effect against arterial stiffness. There are:

Antihypertensive agents

Angiotensin converting enzyme inhibitors (ACEIs)

There are many drugs among this class showed beneficial effects against the AS. Example of ACEIs, is perindopril. The effect of perindopril on the AS is independent to it its antihypertensive effect. In one cross-sectional study included hypertensive patients treated with perindopril, the PWV value is decreased after 2 months of commencing therapy and a further decrease of PWV is observed after 6 months. The effect of perindopril on the arterial stiffness is independent to its effect on the blood pressure particularly after 6 months treatment [50]. The effect of perindopril on the AS was observed after using 4 mg/dl for nine months as it reduces the cfPWV from 11.6 m/s to 7.5 m/s [51].

Angiotensin receptor blockers (ARBs)

A number of ARBs are proved to have a destiffness effect on the blood vessels in elderly patients with essential hypertension, which included 40mg telmisartan; 50mg losartan;80 mg valsartan; and 150mg irbisartan daily by mechanisms independent on their reducing effect of the blood pressure [52]. Long term using of losartan at fixed dose of 50 mg /day, reduces the blood pressure and the value of aortic PWV in aged patients with essential hypertension. This effect is reflecting in reducing the occurrence of acute coronary syndrome [53] while, short term using of losartan (50 mg/d for 4 weeks) does not decrease aPWV in hypertensive patients, while losartan treatment for 16 weeks reduces the aPWV which correlated positively with a decline in the diastolic blood pressure [54].

Olmesartan reduces marginally the baPWV in elderly patients presented with mild-moderate essential hypertension by mechanisms related to the counteracting the oxidative stress and inflammation [55]. The effect of olmesartan on the AS is a dose-dependent effect. olmesartan (80 mg/d) reduces the aPWV by 0.58m/s compared with 0.48m/s after using 20 mg/d in patients with metabolic syndrome [56]. Further study confirmed that higher doses of olmesartan (40 and 80 mg/d) are effective in reducing the PWV compared with a dose of 20mg/day for 52 weeks treatment of hypertensive patients with metabolic syndrome [57]. Olmesartan improves remodeling of the stiffed-blood vessels by acting at the intrinsic elastic properties and independent on its effect on the blood pressure [57].

Beta-adrenoceptor blockers

Metoprolol treatment for 3 months non-significantly reduces the baPWV by 0.1 ± 2.2 m/s despite its significant effects against the biomarkers of regenerative capacity [58]. In healthy subjects, 80 mg single dose metoprolol reduces thebaPWV by a mean value of 0.47m/s after 6 hours of administration, and this effect is related to its hypotensive action [59]. Three-week treatment with bisoprolol (5mg/d) of grade I-II hypertension male patients produced a significant decline of PWV, which accounted a mean value of 1.1 m/s compared with placebo-treated subjects. This

effect is not associated with a significant changes of the AI, and it is related to the reduction of the systolic blood pressure [60].

β- adrenoceptor blocking agents with vasodilator property

Both carvedilol and nebivolol have a beneficial non-significant effect on the aortic stiffness by evidence of reducing the aortic strain, distensibility, stiffness index in stage-I hypertensive patients [61].Carvedilol treatment for 24 weeks reduces the cfPWV similar to the effect of losartan, but it is inferior to the losartan treatment in reducing the AI in hypertensive patients with a mean age of < 50 years [62]. Patients with acute ischemic stroke and a high systolic blood pressure (160-220 mmHg) responded well to short-term treatment with nebivolol (5mg daily) by blood pressure (aortic and brachial), AI and PWV [63]. Combined therapy of nebivolol (5mg daily)and valsartan (160mg daily) up to 12 weeks treatment, is effective in reducing the AI and PWV in hypertensive patients [64]. Celiprolol (100-200mg daily for 12 weeks) is ineffective in reducing the baPWV in hypertensive patient compared with nebivolol despite both drugs reduce central blood pressure [65].

β-adrenoceptor stimulating agents

In experimental animal study, the expression of β2 and β3 receptors were demonstrated in the endothelial cell of the aorta, and stimulation of β2-receptors resulted in a decline of aPWV, which is genetically high in the spontaneous hypertensive rat [66] activation of β3-adrenoceptor did not produce significant effect on the aPWV.

Calcium entry blockers

Examples of destiffness agents are azelnidipine, barnidipine, nitrendipine, felodipine, lercanidipine, and verapamil. Azelnidipineis a low onset and long acting dihydropyridine calcium entry (L and T channels) blocker which used in management of hypertension with a negligible effect on the heart rate. Azelnidipine as add-on-therapy (olmesartan) in a dose of 20 mg/d/over two years, reduces significantly baPWV,AI (from 92.0±4.4% to 83.0 ± 2.7%, and improves the left ventricle dysfunction [67]. Barnidipine is a long acting dihydropyridine calcium entry blocker that useful in management of elderly hypertension [68]. Six-month treatment with barnidipine (10-20 mg once daily) in patients with grade III essential hypertension reduced the AI from 22% to 17% without producing significant changes in the indices of intrinsic AS [69]. Combined therapy of amlodipine with losartan is effective in reducing the AI at heart 75 beat/min and cfPWVwhich are independently related to their hypotensive effects [70]. Amlodipine-valsartan therapy is superior the combination of nifedipine-valsartan in reducing the arterial stiffness, which is independent on the hypotensive effect [71].

Direct renin inhibitors

Oral administration of aliskiren (100-300 mg/daily) to patients with Marfan's syndrome reduces significantly the peripheral baPWV by 1.6m/s, and insignificantly the central aortic PWV by 0.2m/s [72]. Long term therapy (6 months) of aliskiren to elderly hypertensive patients significantly reduces stiffness of the carotid arteries from 6.42 ± 2.34 to 5.07 ± 1.29 m/s compared with hydrochlorthiazide which increased the AS from 5.05 ± 1.78 to 7.25 ± 2.68m/s suggesting the role of renin in inducing arterial stiffness in hypertensive patients [73]. Aliskiren as add-on-therapy to valsartan in patients with hypertension produces further beneficial effect on the arterial stiffness assessed by determination of AI, as well as attenuates the oxidative stress syndrome which assessed by determination of the urinary 8-hydroxyguanisine level [74]. Furthermore, the favorable effects of aliskiren on the aortic AI and PWV are independent to its hypotensive effect, and it associates with a decrease number of endothelial progenitor cells indicating its direct effect on the endothelium of the blood vessels [75].

Thiazide diuretics

Bendrofluzide as perindopril can reduce the blood pressure, and the augmentation index after 10-week treatment of patients aged >60 year and presented with isolated systolic hypertension [76].Combined therapy of indapamide and perindopril for 12 weeks, reduced the AI (by 9.2±13.1 %), and CAVI at right side by 0.6, and at left side by 0.67in middle aged patients with stage II essential hypertension [77]. Moreover, indapamide combined with perindopril reduced the ctPWV by 0.8m/s after 24 weeks treatment of patients presented with grade I-III essential hypertension [78].

Mineralocorticoid receptor antagonists

Aldosterone-to-renin ratio is an important variable that determine the ASas it correlates significantly with blood pressure, PWV, and AI [79]. Spironolactone (50 mg/d for 4 weeks) significantly reduces the aPWV, aAI and aldosterone-to-renin ratio in hypertensive patients compared with bendroflumetazide indicating the role of aldosterone-renin in the pathogenesis of arterial stiffness [79]. Spironolactone therapy for 24 weeks reverse the AS in patients with uncontrolled hypertension as it significantly reduced the cfPWV [80]. Spironolactone at doses <50 mg/d for 24 weeks does not significantly reduce the aPWV in patients at risk of diabetes mellitus [81]. In end-stage chronic kidney disease due to polycystic kidney, spironolactone (50mg/d for 24 weeks) showed insignificant effect on the cfPWV, circulating endothelial cell, and oxidative stress markers [82].

Drugs acting on the epithelial sodium channel (ENaC)

Genetic variation of ENaCis a feature of Black African people who suffered from uncontrolled hypertension and they well responded to amiloride [29]. Low doses of amiloride (a sodium sparing diuretic) can reduce the EnNaC activity leading to a significantly reduction of the arterial stiffness [83]. High blood pressure is normalized within short period (1-4 weeks) and remained controlled with small doses of amiloride (5-10 mg/d) [84]. This effect is associated with improvement of AI, regional PWV, and pulse stiffness ratio. Izzo et al (2019) found that low doses of amiloride can control the blood pressure and reversed the arterial stiffness to become normal after a period of time in patients with hyperaldosteronism [85]. The effect of amiloride is specifically directed against ENaC and not related to its effect against the confounding factors. In experimental study carried on mice fed with western diet, amiloride improves the endothelial function and aortic stiffness without significant effects on the blood pressure, obesity indices, and other biomarkers [83].

Endothelin-A receptor antagonists

Examples of these drugs are Sitaxsentan, BQ-123. Nocturnal dipping of PWV was lost in hypertensive patients due to chronic kidney disease, and it is linked to a significant high serum level of endothelin. Sitaxsentan therapy for 6-week maintained the nocturnal dipping of the blood pressure and restors the changes of PWV during night in hypertensive patients [86]. Sitaxsentan (100mg once daily for 6 weeks) showed a significant arterial destiffness (reduces the PWV by 0.64±0.24 m/s), anti-

proteinuria, and hypotensive effects in chronic kidney disease patients [87].

Vasopeptidase inhibitors

These vasodilators act by inhibiting generation of angiotensin II (by inhibiting angiotensin converting enzyme), and increasing the level of bradykinin (by inhibiting neutral endopeptidase; neprilysin). These drugs are still under investigation for clinical uses in management of hypertension and heart failure. Their antihypertensive effects are not related to race or ethnicity, age, and the status of salt or serum renin level [88]. Examples of these inhibitors are sampatrilat, fasidotril, gemopatrilat and omapatrilat. Adverse reactions of vasopeptidase inhibitors are the main cause of withdrawing these drugs as hypotensive and destiffness agents [89].

Oral antidiabetic agents

Dipeptidyl peptidase inhibitors

In randomized controlled clinical trial using vildagliptin or glibneclaimide, in addition to metformin, showed that these medicines did not improve the arterial stiffness (assessed by augmentation index, PWV, and systolic central pressure) in patients with T2D and hypertension after twelve week treatment [90]. In other double blind randomized placebo0controlled clinical trial, saxagliptin marginally improves the arterial stiffness after 12 week treatment [91]. Sitagliptin as an add therapy, improves the glycemic indices accompanied with a decrease of abPWV by 10 cm/s after 24 months treatment. This observation indicates that dipeptidyl inhibitors have a marginal effect on the arterial stiffness and their effects will establish after a long period of treatment [92].

Sodium glucose co-transporter 2 inhibitors

This group of antidiabetics acts on the transport system of glucose at the renal tubule which enhancing the glucose excretion in the urine and thereby reducing the serum glucose level [93]. Empagliflozin and canagliflozin belonged to this group and proved to be having less adverse reactions compared with others beside they have cardio-protective effects [94,95]. There is an evidence that these drugs improve the arterial dysfunction. Empagliflozin reduces the rf-WPV during euglycemia and hyperglycemia, while it reduces the cf-PWV during hyperglycemia using modified glucose clamp technique [96]. In patients with T2D,dapagliflozin reduces the PWV from 10.1 ± 1.6 m/s to 8.9 ± 1.6 m/s, irrespective to its effect on the blood pressure [97]. Empagliflozin alone or as a top on metformin treatment improves the cfPWV by approximately 15% compared with metformin treatment alone in T1D patients [98]. Moreover, empagliflozin on the top of metformin treatment reduces the carotid pulse velocity (known as β-stiffness) by 36% compared with metformin treatment alone [98].

Lipid lowering agents

There is no doubt that stains exert beneficial effects on the vascular smooth muscle, and their effects related to the property of lipophilic of the statins [99,100]. Moreover, the effect of simvastatin seems to be transient by the evidence that middle age patients treated with 40mg simvastatin showed a significant decrease of AI after 12 months, and this effect did not persist after 18 months of treatment [101]. Moreover, the effect of simvastatin on the central blood pressure and AS does not relate to the primary action of simvastatin in reducing the circulating lipid profile [101]. In experimental molecular study, Lampi et al (2016) showed that simvastatin attenuates the phosphorylation of the myosin light chain and the activity of RhoA which is usually increased in the matrix of the stiffed artery [102]. Moreover, simvastatin enhanced the activity of Rac 1 which improved the reorganization of the matrix and thereby improved the endothelial function [102]. Rousavastatin (10mg/day for 8 weeks) significantly reduced the baPWV in patients with coronary artery disease, which is related to its effect against the rho/rho kinase signalling, and not related to its effect on the circulating lipid profile [103]. Patients with stable atherosclerosis treated with atrovastatin (80mg/d) showed a significant decrease of circulating rho/rho kinase leucocyte which observed after two weeks treatment and persisted at the end of 4 weeks treatment [104]. The effect of statins on the rho/rho kinase is not correlated with the changes in the circulating lipid profile [104]. Koniari et al (2016) demonstrated the beneficial effect of simvastatin on the AS of blood vessels of rabbits fed with atherogenic diet by an evidence of attenuating the neointima hyperplasia through its effect against the oxygen and nitrogen reactive species [105].

Pravastatin treatment did not improve the structure and the function of the blood vessels assessed by determining the intima-media thickness of common carotid arteries, as well as the aortic stiffness in hyperlipidemic patients treated with human immune-deficiency virus medications [106]. The effect of statins (simvastatin, rousovastatin. pravastatin, and atrovastatin) on the baPWV was found to be not related to the duration of using statins and this effect did not show significant difference between normotensive with hypertensive patients with coronary artery disease [107]. Ichihara et al (2005) suggested that long term using of fluvastatin, significantly reduced the PWV compared with simvastatin which its effect is transient, and pravastatin which did not produce any significant effect in uncontrolled hypertensive-dyslipidemia patients [108]. Long term (> 3 months) and extensive (high doses) pravastatin therapy can reduce the AI in hypercholesterolemic patients, which related to the reducing level of low density lipoprotein [109]. Comparing with ezetimibe, a lipid lowering agent that inhibits the absorption of intestinal cholesterol, statins are more effective in reducing the PWV and augmentation index of the AS [110].

Recent study utilizing atomic force microscope analysis found that statins through their cholesterol depleting effect in the arterial wall, can remodel the vascular smooth muscle orientation which ultimately decrease the arterial stiffness and improve the blood vessel function [111].

Nitric oxide (NO) donors

This group including Nitroglycerin, Isosorbide mono-and dinitrate, Naproxinod, Molsidomine, Linsodimine. NO donors through their effect of releasing nitric oxide (exogenous) can reduce the risk of thrombosis. Inhibiting the platelet aggregation, and slowing the progression of atherosclerosis. Any condition that reduces the bioavailability of endogenous NO can contribute in the development of resistant hypertension and thereby AS [112]. Acute administration of nitroglycerin (0.3mg sublingually) in healthy subjects produces a significant effect on the muscular arteries by the evidence of reducing a mean value of the CAVI (1.26), and stiffness of the aorta at heart-thigh β (1.14) and thigh-ankle β (3.69) [113]. Moreover, the effect of acute administration of nitroglycerin produces significant effect on the in both healthy subjects and patients with coronary artery disease It reduces the stiffness of the aorta and the CAVI by a mean value of 3, and 10, respectively after 5 minutes of

administration [114]. In experimental anaesthetized animals, nitroglycerin infusion reduces vascular resistance by dilating the conduit vessels as it reduces the femoral artery resistances and the heart-aorta PWV, which is independent to its effect on the blood pressure [115]. Naproxcinodis a nonselective cyclooxygenase enzyme inhibitor, has analgesic, and anti-inflammatory properties. It is metabolized into naproxen and nitroxybutyl ester, which associated with releasing of NO. In experimental animal study, naproxcinod has a significant beneficial effect on the heart and blood vessels as it improves the ejection fraction and reducing the blood pressure in mouse model of Duchenne's muscular dystrophy [116]. Molsidomine treatment for 12 months improves the endothelial function in patients with angina pectoris through its property of donating nitric oxide [15]. In experimental animal study, molsidomine increases the cardiac fractional shortening, and decreases the end systolic and end diastolic ventricular diameter, in addition to its effect against the atherosclerosis plaque which becomes more stable [117].

Advanced glycated end-products cross-link breakers

These drugs act directly on the blood vessels structure e.g. Amino guanidine, Alagebrium chloride. Advanced glycated end-products (AGEs) are accumulated in the blood vessels leading to increase collagen cross-linking property, and thereby increasing the AS. This process is running in the irreversible fashion. Amino guanidine (Pimagedine) acts by inhibiting diamine oxidase and nitric oxide synthase enzymes. It blocks the formation of the AGEs by interacting with 3-deoxyglucose. Amino guandine expressed a beneficial effects in reducing the arterial stiffness in both experimental and clinical studies [118-121]. In vivo and in vitro experimental studies, 4-week treatment with amino guanidine reversed the increasing value of aortic PWV due to ageing process and the mechanical arterial stiffness [122]. A non-reproducible results were observed with alagebrium (3-phenacyl-4,5-dimethylthiazolium) chloride as destiffness medicine in the experimental and clinical studies [123-126]. In a small sample size clinical study, alagebrium chloride reduced the carotid AI and enhanced the flow mediated dilation in patients presented with isolated systolic hypertension. These effects are inversely related to the biomarkers of the collagen synthesis [127].

Xanthine oxidase inhibitors

High serum level of uric acid is dependent on the existence of the cardiovascular risk factors, including high blood pressure, diabetes mellitus, obesity and dyslipidemia. Therefore, As is closely associated with increase serum uric acid, partly due to the coexisting of cardiovascular risk factors, and partly due to the inflammation and/or oxidative stress that induced by uric acid [128]. Drugs that suppress the activity of xanthine oxidase enzyme and thereby the production of uric acid, can reduce the arterial stiffness. Xanthine oxidase inhibitors (e.g. allopurinol) improves the elasticity of the blood vessels by suppressing the inflammation and/or oxidative stress mediators, and the EnNaC activity which implicated in the AS [129-131].

Mitochondrial targeting antioxidant (MitQ)

This product is consisting from natural antioxidant with a lipophilic cation to allow crossing the cell membrane [132]. This product act by reducing or counteracting the mitochondrial reactive oxygen species [133]. Experimental studies showed that 4-week oral administration of MitQ significantly reduces the aortic stiffness (i.e. reduce aortic PWV) in old but not young mice [134,135]. Oral administration of MitQ (20mg once daily for 6-week) reduces the cfPWV in subjects with a high baseline value of cfPWV (> 7.6 m/s due to ageing and/or high systolic blood pressure) compared with subjects having cfPWV<7.6 m/s [136]. This beneficial effects may be related to the anti-inflammatory (by the evidence of reducing the creactive protein, and interleukin-6) and/or antioxidant (by reducing the level of oxidized low density lipoprotein) effects [136].

Others

Red wine

Drinking of red wine (12% alcohol) reduces the blood pressure and arterial compliance after ingestion in healthy subjects[137]. Acute ingestion of red wine, but not dealcoholized red wine, reduces the PWV in healthy subjects independently to its reducing effect on the blood pressure [138]. There is no clinical evidence that this effect is of significance in patients with AS.

Coccao Products

Acute or chronic consumption of cocoa products significantly decreased the PWV (2.7 versus 0.33 m/s) and AI (4.7 versus 4.5), respectively, regardless the age of the healthy participants [139].

Curcumin

It improves the bioavailability of the endogenous NO, and thereby improves the vascular blood flow. Its action as arterial de-stiffing seems to be selective as it improves the arterial function in young healthy obese subjects but not in the elderly people with arterial stiffness [140,141].

Omega 3 Fatty Acids

Fish oil supplementation (contained n-3 fatty acids) for 8-month significantly reduces the AI in rheumatoid arthritis patients presented with AS [142]. Dietary supplementation with higher content of palmitoleic acid and arachidonic acid showed a significant lower AI. In controlled double blind clinical trial carried on healthy subjects, 6 g daily supplementation of fish oil containing 480mg eicosapentaenoic acid and 480mg docosahexaenoic acid significantly reduced AI, i.e. reduced the aortic stiffness [143]. Omega-3 fatty acids supplementation attenuated the arterial stiffness because it can overcome the endothelial dysfunction through its pleiotrophic effects including, antioxidant, anti-inflammatory and anti-dysmetabolic [144].

Vitamin D

Patients with end-stage chronic kidney disease presented with arterial stiffness did not response to the vitamin D analogue as cfPWV did not significantly change [145]. There is evidence that for each 1ng/ml serum vitamin D decrease, there is an increase of cardio-ankle vascular index by +0.04 m/s [146]. Chen et al (2019) concluded in their meta-analysis study that vitamin D supplementation (3000 IU/daily for > 4months) improved the arterial stiffness in patients with nutritional vitamin D deficiency, indicating the indirect effect of vitamin D on the smooth muscle cell [147].

Anti-inflammatory drugs

These drugs act on the structure as well as the hemodynamic function of the blood vessels e.g. corticosteroids, TNF-α antibodies, Aspirin

Conclusion

Arterial stiffness is a normal physiological process of ageing and it accelerated by high blood pressure or presence of any component of metabolic stress syndrome. Several Mechanisms are involved in pathogenesis of arterial stiffness, and there is no pharmacological therapy that can overcome all these mechanisms at the same time. There are several factors that determine the effectiveness of destiffness medicines, including dosage regimen, duration of therapy, using combination therapy, presence of metabolic syndrome components, the status of renin-angiotensin-aldosterone pathway racial and genetic factors, and other predisposing or risk factors. Therefore, there is no unique destifness drug that reverse directly the arterial stiffness.

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