Arterial Ageing

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The ageing of humans and its physiological consequences is regulated by both genetic factors, as selected by evolution, and environmental factors, for example, the influence of nutrition and caloric intake with its mitochondrial effects. Some of the mediating mechanisms have been characterised, but much is still unclear. As biological ageing is central to understand the development of many chronic disease conditions that increase in incidence with advancing chronological age, it is important to understand age-related mechanisms in order to find new ways to dissect the causality of disease and even to find new targets for preventive efforts. In the cardiovascular system, the development of disease is paralleled by age-associated changes, and these will be further discussed, with a focus on arterial ageing [1]. It is sometimes not easy to disentangle the pathological changes in the arterial tree from these changes that are age related in themselves, for example, related to atherosclerosis that increases in prevalence in large arteries with advancing age, at least in western populations.

14.1 Composition and Function of the Arterial Wall

The arterial wall consists of three distinct layers, from inside and out, the *tunica intima* (made up mainly by endothelial cells), *tunica media* (which is made up of smooth muscle cells and elastic tissue) and *tunica externa* (composed of connective tissue made up of collagen fibres). These layers are innervated by the autonomous

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nervous system and involved in the modification of arterial function following the propagation of the pulse wave from the heart with every heartbeat.

The endothelium is closest to the blood stream circulating in the arterial lumen and involved in regulating vasodilation and vasoconstriction by secretion of vasoactive substances such as nitric oxide (NO), endothelin and many more [2]. With ageing, the endothelial function starts to deteriorate, and less NO is produced by impaired induction of endothelial NO synthetase (eNOS). In addition the normal insulin sensitivity in the endothelial cells, associated with vasodilation by the hormone insulin in the postprandial state, is replaced by a gradual increase in endothelial insulin resistance [3]. This will lead to a loss of the vasodilatory capacity induced by insulin and therefore vasoconstriction and blood pressure elevation, another mechanism by which insulin resistance (resulting in hyperinsulinaemia) might lead to hypertension [4]. Furthermore, endothelial dysfunction is associated with reduced anticoagulant properties as well as increased adhesion molecule expression, chemokine and other cytokine release, promoting inflammation, in addition to reactive oxygen species (ROS) production from the endothelium. This leads to local inflammation with myofibroblast migration and proliferation inside the vessel, often linked to vascular remodelling. In addition perivascular inflammation can contribute to local vasoregulation. These factors taken together play important roles in the development of atherosclerosis, starting in the intima with fatty streaks and lipid deposits already at an early age in risk individuals [5], for example, with familiar hypercholesterolaemia.

The media of the artery consists of layers of elastic elements that are stretched by each pulse wave in systole and will be flexed back in diastole, thus contributing to a smooth forward propagation of the blood stream in both systole and diastole (so-called Windkessel effect). These elastic elements consist of elastin, a protein that is preformed in fetal life and decreases gradually during the lifespan. Another component is collagen as well as the smooth muscle cells causing contractions. The third, outward layer (tunica externa) is surrounded by perivascular fat in different amounts, with its own cytokine activities for local inflammation.

14.2 Age-Related Changes of Arterial Properties

During ageing the collagen content will become relatively increased, and cross-links will occur between collagen elements, also influenced and further enhanced by glycation of arterial wall proteins. The consequence of these two developments, a relative decrease in elastin and a corresponding relative increase in collagen (with cross-linkages and glycation), will contribute, together with impaired endothelial function, to a gradual stiffening of the large (elastic) arteries. This is in contrast to the medium-sized (muscular) arteries that will not undergo the same age-related changes. Therefore the aorta and the carotid arteries will show typical age-related increasing stiffness, while this is not the case for the brachial arteries. The changes of the femoral arteries are somewhat in between, with a notable stiffening taking place with ageing but not as pronounced as in the aorta. These arteries can also be

affected by atherosclerosis, similar to what happens in the aorta and carotid arteries, but in contrast to the brachial artery that is not affected.

This gradual age-related stiffening of the large elastic arteries is named *arteriosclerosis* and occurs mainly in the media of the artery but is further facilitated by endothelial dysfunction. In addition, it is believed that haemodynamic stress; metabolic factors, most importantly hyperglycaemia; and chronic inflammation could contribute to this process. On the other hand, the development of *atherosclerosis* involves first of all the intima and later on also other layers of the artery, with well-described morphological changes [5]. The consequence could later on be incidence of cardiovascular disease events caused by atherosclerosis, for example, ischaemic heart disease (IHD), stroke or peripheral artery disease (PAD). These manifestations constitute the major public health problem in western societies and in a growing proportion of the population in developing countries according to the World Health Organization (WHO).

According to one hypothesis, arteriosclerosis starts very early in life and is influenced by fetal programming of the vasculature and its elastin content [6]. Later on the process of atherosclerosis starts and runs in parallel with arteriosclerosis. The clinical events are usually linked to atherosclerosis, based on its derived plaque formation and rupture, even if arterial stiffness has also been shown to be an independent predictor of future cardiovascular events and mortality, based on recent meta-analyses [7, 8]. In both conditions, oxidative stress, chronic inflammation and increased activity of the renin-angiotensin-aldosterone system (RAAS) seem to be of considerable importance.

14.3 How to Evaluate Arterial Function and Arterial Ageing?

The arterial function associated with ageing and the morphological changes in the arterial wall can be measured by use of different technical methods, from more simple to more sophisticated ones. Brachial blood pressure undergoes typical changes with ageing, at least in most populations. There is a constant increase in systolic blood pressure in both men and women, but a steeper relative increase in women at around the time of menopause. The diastolic blood pressure tends to increase until age 60–65 years and then flattens off or even decreases. This means that the pulse pressure will show an increasing trend from around 50 years, and this is a reflection of underlying arterial stiffness. Similar changes occur in the central circulation and are possible to measure indirectly by so-called pulse wave analysis (PWA) in the radial artery based on tonometry and an algorithm. A specific characteristic of the central blood pressure is that it tends to be lower than the peripheral blood pressure in younger subjects, and therefore a blood pressure amplification can be registered from the central to the peripheral blood pressure. This amplification is lost in midlife, and after that the central and peripheral pressures tend to be rather similar with few differences [9].

Of utmost importance to arterial ageing is the increase in pulse wave velocity (PWV) that occurs as a reflection of increasing arterial stiffness caused primarily by

the morphological changes with relatively less elastin and more collagen (and cross-linkages) in the arterial media layer. In most cases PWV is measured directly along the aorta from the carotid to the femoral artery as c-f PWV [9]. In some circumstances it has also been proposed to measure PWV between the brachial artery and the femoral artery (b-f PWV) or the ankle arteries (b-a PWV), but this method involves muscular arteries (*art. brachialis*, *art. tibialis posterior*, *art. dorsalis pedis*) with less elastin content and is therefore less informative. However, in the Far East (Japan, China), cultural norms may preclude observers to measure stiffness in the groin via direct access to *art. femoralis*, that is why other more distal arterial alternatives are preferred. Based on a European study of several population-based cohorts, a group of about 1,400 healthy, normotensive subjects were used for definition of the age-specific normal range of c-f PWV [10]. Based on these data, a threshold for pathological c-f PWV and increased cardiovascular risk was first defined as >12 m/s [10], but after a revision in 2012 as >10 m/s [11]. This means that an increased c-f PWV is a marker of arterial stiffness affecting the large elastic arteries, and this biomarker has also been shown to predict not only cardiovascular morbidity and mortality but also total mortality in recent meta-analyses [7, 8].

14.4 The Concept of Early Vascular Ageing (EVA)

In recent years the interest in arterial stiffness has increased, as well as in the underlying *arteriosclerosis*, as a precursor to the more well-known and well-studied *atherosclerosis*, with its pathology influenced by genetics, high LDL cholesterol levels, smoking, hypertension, inflammation and overt type 2 diabetes [5]. In many cases it is believed that early life programming may cause a susceptibility for this increased tendency for arterial stiffening as well as other aspects of vascular tree, for example, the development of capillaries and the microcirculation. As this process is also related to ageing, it has been proposed that a process of early vascular ageing (EVA) is an early sign of arteriosclerosis (in the media) but linked also to early changes in the endothelial function (intima), haemodynamic changes and the influence of abnormal glucose metabolism and increased inflammation [12–14]. The difference between the concept of arterial ageing and EVA is that the latter also encompasses the smaller arteriolae and the microcirculation, based on the crosstalk between the macro- and microcirculation [14]. EVA is now being extensively studied in different population-based cohorts, both in Europe and in Latin America, but still no general definition has been agreed upon. One way to define EVA could be to use the outliers according to the normal range of c-f PWV, i.e. above the two standard deviations (SD) of the normal distribution of c-f PWV in the European reference group [10] (Fig. 14.1). Another way to describe EVA is based on statistical methods when arterial stiffness (c-f PWV), a central aspect of EVA, is used as the dependent variable in multiple regression analyses and a number of risk markers are used as independent variables, based on data from population-based studies. As the influence of haemodynamic changes and sympathetic nervous system (SNS) stimulation on the arterial tone is substantial, the data are normally adjusted for mean arterial pressure

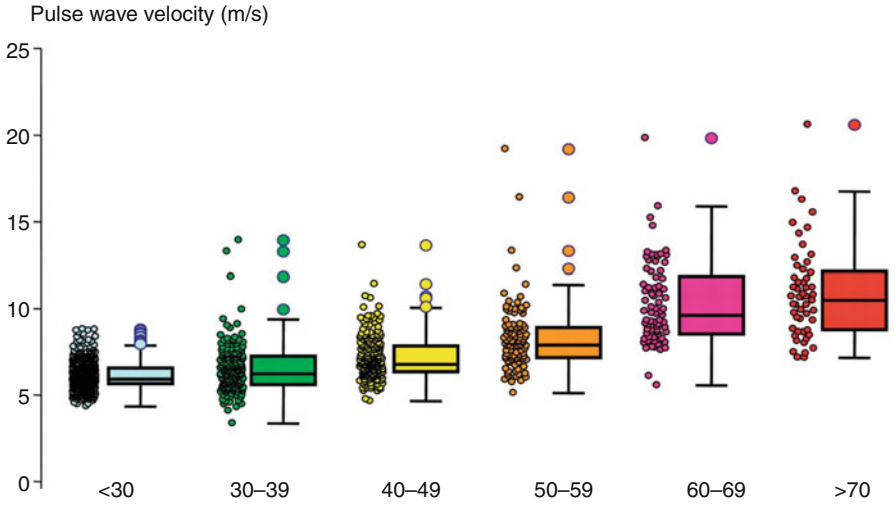

Fig. 14.1 Normal values for pulse wave velocity (c-f PWV): average according to age (1,455 healthy, normotensive subjects). *Boxes* contain 50 % of the data and *bars* contain the remainder (2 SD); *horizontal lines* indicate medians and the *circle* indicates outliers (From: The Reference Values for Arterial Stiffness' Collaboration [10])

(MAP) and heart rate (HR), the latter as a marker of SNS activity. Such investigations in a population-based study in Malmo, Sweden, have revealed that markers of glucose metabolism and dyslipidaemia (elevated triglycerides, low HDL cholesterol levels), as well as waist circumference (a marker of active abdominal fat tissue with inflammatory action), are significantly associated with arterial stiffness, but not LDL cholesterol, smoking or cystatin-C, a marker of impaired renal function [15]. The findings thus point to different clusters of cardiovascular risk factors involved in the development of arteriosclerosis and atherosclerosis, respectively.

Still there is a need to better define EVA in different age groups but also in relation to gender and ethnicity, as well as based on genetic studies for improved classification [16]. Some would argue that EVA is just a construct to cover one example of target organ damage (arterial stiffness) in subjects at high cardiovascular or metabolic risk and primarily influenced by haemodynamic changes and blood pressure levels. However, the modern genetics of hypertension and blood pressure regulation, based on a global study, could not show any marker on chromosome 13 [17], but exactly on this chromosome, a genetic locus (for the *COL4A1* gene, involved in collagen metabolism) was found for arterial stiffness in a study from Sardinia, Italy, with independent replication in another American cohort [18]. This shows that even if arterial stiffness (and EVA) is strongly influenced by the blood pressure load (MAP), HR and SNS activity, there could even exist some other important components (collagen protein synthesis, structure) and vascular risk factors (hyperglycaemia, dyslipidaemia, inflammation) independent of blood pressure regulation. If true, this opens up new possibilities to target these mechanisms of protein/collagen synthesis with new drugs to reduce arterial stiffness.

So far it has been shown that a prolonged control of hypertension will reverse early changes and have a long-term beneficial influence on arterial stiffness with decreasing c-f PWV levels over time, beyond the blood pressure control itself [19]. However, an ongoing randomised controlled study in France (SPARTE) aims to compare a treatment strategy for reduction of arterial stiffness (c-f PWV) by different means, including drugs that specifically influence the renin-angiotensin system, and another treatment strategy (control) to go for implementation of control of the conventional risk factors including blood pressure, as suggested in the guidelines [20]. SPARTE is supposed to continue for still a number of years until a sufficient number of cardiovascular end points have accumulated to show potential differences in outcomes between the treatment arms. Recruitment is ongoing.

14.5 Haemodynamic Effects of Vascular Ageing: Blood Pressure

As arterial stiffness is a characteristic of vascular ageing based on morphological changes in the arterial wall, there is also a need to better understand its haemodynamic consequence. A starting point is to try to list different characteristics of haemodynamic ageing and to try to understand the association with underlying morphological changes in the arteries (Table 14.1).

Well-known changes, as already alluded to, include an increase in brachial systolic blood pressure and a flattening off of the diastolic blood pressure to be followed by a decrease in diastolic blood pressure above the age of approximately 60–65 years. This will lead to increased risk of isolated systolic hypertension (ISH) and elevated pulse pressure, both conditions being associated with increased prospective risk of cardiovascular events [21]. The same holds true for corresponding

Table 14.1 Examples of haemodynamic ageing and its relationship to blood pressure (BP) and arterial stiffness

Age-related changes in brachial BP
Isolated systolic hypertension (ISH)
Elevated pulse pressure (PP)
Age-related changes in central BP
Increased central systolic BP and PP
Increased BP variability
Linked to arterial stiffness
Decreased heart rate variability (HRV)
Linked to arterial stiffness
Impaired endothelial function
Less vasodilation, linked to arterial stiffness
Impaired baroreceptor function, orthostatic hypotension
Linked to arterial stiffness
Microvascular disease in diabetes
Influenced by long-standing hyperglycaemia

changes in central systolic blood pressure and pulse pressure, because around the chronological age of 50 years, the blood pressure amplification between the central and peripheral circulation decreases, and thus central and brachial blood pressures tend to become more similar. These changes according to conventional blood pressure and central blood pressure recordings have previously been discussed in detail by Stanley Franklin et al. [21, 22]. For example, in participants from the Framingham Heart Study who were free of CVD events and antihypertensive therapy, in all 1,439, CVD events occurred between 1952 and 2001. In pooled logistic regression with the use of BP categories, combining SBP with DBP and PP with mean arterial pressure (MAP) improved model fit compared with individual BP components. Significant interactions were noted between SBP and DBP ($p=0.02$) and between PP and MAP ($p=0.01$) in multivariable models. The combination of PP + MAP (unlike SBP+DBP) had a continuous relation with cardiovascular risk and may provide greater insight into haemodynamics of altered arterial stiffness versus impaired peripheral resistance but is not superior to SBP+DBP in predicting CVD events [21]. This analysis is based on conventional blood pressure variables, but reflecting the age-related changes that more modern and sophisticated technologies can reveal.

14.6 Arterial Stiffness and Age-Related Haemodynamic Changes

Some other features of haemodynamic ageing are less well characterised, but all linked to arterial stiffness as an underlying contributing factor, and thereby also explaining most of the risk associated with these different features. One of them is increased blood pressure variability (BPV), linked to increased cardiovascular risk, i.e. for stroke [23]. Increased BPV can be evaluated on a visit-to-visit basis with weeks or months between visits but also based on shorter time intervals (days, hours, even beat-to-beat timing), as recently reviewed by Gianfranco Parati et al. [24]. An underlying feature is arterial stiffness, and it is reasonable to believe that this factor might explain most of the increased risk associated with increased BPV, even if also some mechanical changes could play a role based on changes in blood flow, shear stress or transmission of increased pulse wave energy to small arteries and the peripheral circulation [24].

In a corresponding way, it has been reported that a decrease in heart rate variability (HRV) is a marker of ageing and increased cardiovascular risk but also associated with increased arterial stiffness, for example, in patients with type 1 diabetes [25]. The decrease in heart rate variability is supposed to be influenced by an imbalance between the sympathetic and parasympathetic parts of the autonomous nervous system.

Furthermore, it is well known that episodes of orthostatic hypotension are associated with increased cardiovascular risk during follow-up, based on data from several epidemiological studies. Also here we notice underlying arterial stiffness as a common denominator, as shown in the Rotterdam study of elderly subjects [26]. The link could be the impaired stretching (compliance) of the carotid arterial wall

close to the baroreceptor due to arterial stiffness and superimposed atherosclerosis, leading to impaired baroreceptor function in response to change of body position. This could contribute to the understanding of arterial stiffness being the true risk marker behind orthostatic reactions, often seen in aged subjects with, for example, diabetes of long duration. These orthostatic reactions should be separated from benign vasovagal reactions with orthostatic reactions in younger subjects.

It is conceivable to think that more widespread changes in innervation and the autonomous nervous system could contribute to the ageing of the neural system and thus linked to vascular ageing and decreased baroreceptor function as well as imbalance between sympathetic and parasympathetic activity. In one recent study, the relationship was tested between direct measures of sympathetic traffic and PWV in healthy humans [27]. The authors examined MSNA (microneurography), PWV (Complior® device), heart rate and blood pressure in 25 healthy male participants (mean age 43 years). It was reported that PWV correlated significantly with age ($r=0.63$), SBP ($r=0.43$) and MSNA ($r=0.43$) but not with BMI, waist circumference, waist-to-hip ratio, heart rate, pulse pressure or DBP. Multiple linear regression analysis revealed that only age and MSNA were linked independently to PWV ($r^2=0.62$, $p<0.001$), explaining 39 and 25 % of its variance, respectively. Individuals with excessive PWV had significantly greater MSNA than individuals with optimal PWV. Thus the relationship between MSNA and PWV is independent of age, BMI, waist circumference, waist-to-hip ratio, heart rate, pulse pressure or blood pressure [27]. This shows the contribution of neurophysiological ageing to vascular ageing.

In the arterial wall, there is a crosstalk between the sympathetic nervous system and the renin-angiotensin system that will further decrease elasticity and promote vascular ageing [28].

14.7 Cardiac-Arterial Coupling Influenced by Arterial Stiffness

Finally, it is self-evident that haemodynamic changes associated with ageing are not possible to describe without taking cardiac changes into account. In fact, there is a so-called cardiac-arterial coupling process that can be illustrated by echocardiography examinations [29]. In the end there is thus a crosstalk between cardiac function, as well as morphological changes, and the general circulation in the arterial tree. With increasing stiffening of the proximal thoracic aorta, the reflex wave from the periphery back to the central circulation and the heart can no longer be accommodated, even if the aorta root widens. Instead this pulse wave energy will impact on the heart with increased pressure waves and augmentation during systole leading to increased strain on the left ventricle, causing left ventricular hypertrophy (LVH), and a decreased perfusion pressure during diastole, leading to impaired blood flow in the coronary circulation. These two trends combined will increase the risk of morphological changes (LVH) in combination with coronary ischaemia, thus increasing the risk of CHD events. This is therefore a haemodynamic mechanism

explaining some of the risk potential of arterial stiffness, as measured by increased PWV, for the development of CHD. It contributes to what has been called the cardiovascular ageing continuum by O'Rourke et al. [30].

14.8 Metabolic Syndrome and Arterial Stiffness

Even if it has been difficult to show a strong independent association between arterial stiffness and overt type 2 diabetes [31], there is evidence to show that hyperglycaemia as a continuous variable contributes to vascular ageing and arterial stiffness [32]. Diabetes mellitus was associated with c-f PWV in 52 % of studies in one meta-analysis, but the strength of the association was low [31]. Within the so-called metabolic syndrome (MetS), a number of risk factors tend to cluster, including hypertension, hyperglycaemia, dyslipidaemia (elevated triglyceride, decreased HDL cholesterol), increased waist circumference and underlying insulin resistance. Specific clusters of MetS components impact differentially on arterial stiffness (PWV). Recently, in several population-based studies participating in the MARE (Metabolic syndrome and Arteries REsearch) Consortium, the occurrence of specific clusters of MetS differed markedly across Europe and the USA. Based on data from 20,570 subjects included in nine cohorts representing eight different European countries and the USA in the MARE Consortium, MetS was defined in accordance with NCEP ATPIII criteria. PWV measured in each cohort was "normalised" to account for different acquisition methods. The results could show that MetS had an overall prevalence of 24.2 %. MetS accelerated the age-associated increase in PWV levels at any age and similarly in men and women. Therefore, different component clusters of MetS showed varying associations with arterial stiffness (PWV) across these nine cohorts [33].

Also in a local study from the Malmö Diet Cancer cohort, hyperglycaemia and dyslipidaemia showed independent associations with arterial stiffness in elderly subjects with mean age of 71 years [15].

14.9 Kidney Disease, Inflammation and Stiffness

It is well known that advanced chronic kidney disease is associated with vascular changes, as media sclerosis, and thus increasing arterial stiffness [34]. This is linked to oxidative stress and chronic inflammation [35, 36]. Uraemic toxins, particularly those associated with dysregulated mineral metabolism, can drive vascular smooth muscle cell damage and tissue changes that promote vascular calcification but may also promote DNA damage [36]. Epidemiological data suggest that some of these same risk factors in chronic kidney disease (CKD stages 1–5) associate with cardiovascular mortality in the aged general population. The advanced arterial changes in CKD thus resemble that of a fast progressing vascular ageing. This will further increase the overall cardiovascular risk that is very high in patients with CKD-5 and end-stage renal disease (ESRD).

14.10 Arterial Stiffness in the Elderly

The cardiovascular risk increases rapidly with advancing chronological age, based on arterial stiffness, advancing atherosclerosis and haemodynamic changes in the elderly [37, 38]. On the other hand, survival selection bias may influence the fact that some elderly subjects have survived in spite of advanced arterial stiffness. Epidemiological studies have thus shown that c-f PWV is a stronger risk marker in middle-aged as compared to elderly subjects [8]. No intervention studies exist so far to show the benefits of reducing arterial stiffness (PWV) in the elderly, as was already shown for control of hypertension in 80+-year-old subjects in the placebo-controlled HYVET trial [39].

Another aspect of great interest is the role of chronic inflammation and oxidative stress that are closely linked to the ageing process in general and therefore visible in elderly people [40]. If inflammation can be reduced, a reduction of arterial stiffness has been shown, for example, in patients with inflammatory bowel disease [41], a finding of great theoretical and practical importance. More studies should aim for control of inflammation to prevent cardiovascular disease, but still convincing human studies are lacking.

Arterial stiffness is also a reflection of biological and functional ageing in general. In the Whitehall II study in London, this has been investigated. Researchers aimed to analyse associations of arterial stiffness with age, subjective and objective measures of physical functioning and self-reported functional limitation [42]. Pulse wave velocity was measured by applanation tonometry among 5,392 men and women aged 55–78 years. Results showed that arterial stiffness was strongly associated with age (mean difference per decade: men, 1.37 m/s; women, 1.39 m/s). This association was robust to individual and combined adjustment for pulse pressure, mean arterial pressure, antihypertensive treatment and chronic disease. One SD higher stiffness was associated with lower walking speed and physical component summary score and poorer lung function adjusted for age, sex and ethnic group. Associations of stiffness with functional limitation were robust to multiple adjustments, including pulse pressure and chronic disease. The authors concluded that the concept of vascular ageing is reinforced by the observation that arterial stiffness is a robust correlate of physical functioning and functional limitation in early old age [42]. Why this is so merits further studies.

14.11 Future Perspectives

The development of the EVA concept [12–14] has also triggered research and interest in some other related biomarkers and in haemodynamic ageing [43]. Telomeres represent the end segment of the DNA helix with a shortening taking place with every cell division and therefore regarded as a marker of the biological clock of ageing [44, 45]. Even if discrepant results have sometimes been published, most studies

support the notion that telomere length, or rather the telomere attrition rate over time, could represent an interesting aspect of vascular ageing [44, 45]. Previous studies have shown an association between telomere length and arterial stiffness, as measured by pulse pressure [46].

Other biomarkers of growing interest are, for example, aldosterone and vitamin D, both with implication for cardiovascular ageing. Studies have shown that elevated aldosterone levels are associated with cardiovascular changes including sclerosis and increase stiffness [47]. This is possible to counteract by use of aldosterone antagonist, for example, spironolactone or eplerenone. Large-scale intervention studies are needed before conclusions can be drawn regarding the reversibility of these changes.

Growing evidence has documented that vitamin D deficiency could play a role in the development of pathological changes within the arterial system. Observational studies have shown an increased risk associated with vitamin D deficiency, but it has been hard to show benefits by vitamin D supplementation [48]. Therefore, the role of vitamin D is still somewhat enigmatic in arterial disease.

In the future, more studies should elucidate on the role of arterial stiffness in relation to cognitive decline and risk of dementia, as an association exists between impaired arterial compliance, arterial stiffness, mild cognitive impairment and the occurrence of so-called white matter lesions (WML) in the cerebral white matter [49]. Probably the pulse wave propagation from the general circulation, with stiff arteries, cannot be accommodated in a normal way in the cerebral microcirculation. This leads to micro-bleeds and the development of tissue scaring and WML, a common finding in subjects with uncontrolled hypertension. Hypertension was observed in a Swedish study of 70-year-old people to predict dementia, both of the vascular type and Alzheimer-like dementia [50]. In a recent statement from the American Heart Association/American Stroke Association, risk factors for cognitive impairment have been discussed, including the role of hypertension [51].

Finally, intervention studies are needed to show the benefits of reducing arterial stiffness, over and above blood pressure control per se. In this respect new drugs will also be tested, for example, the vascular protection believed to be an effect of compound 21, a specific angiotensin-2 (AT2) receptor agonist [52], soon to be tested also in humans. Animal studies have been promising in showing a reduction of arterial stiffness, without significant effects on blood pressure in a mouse model [53]. Other new experimental drugs are being developed for vascular protection and blood pressure control [54] and could be combined with more traditional drugs for control of hypertension and hyperlipidaemia. A novel approach is also to retard ageing via influencing mammalian Sir2 (SIRT-1, a NAD+-dependent deacetylase), previously shown to extend the lifespan of lower organisms. This is a promising target molecule to influence some aspects of vascular ageing, and drug development is underway [55]. In summary, arterial ageing is a fruitful concept to be explored for new understanding of vascular biology and new mechanisms for potential intervention.

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