Section A -Research paper

Cognitive Function and Hemodynamics changes in Geriatric

Hossam Abdelbaqy Ismail[1], Mohammed Shehta Tawfik[1], Ramzi Saleh Saleem Alrutbi[2], Ahmed Mohammed Fahmi[1]

[1]Department of Anesthesia, Intensive Care and Pain management, Faculty of Medicine, Zagazig University, Egypt

[2]Department of Anesthesia, Intensive Care and Pain management, Faculty of Medicine, Tripoli University, Libya

Corresponding author: Ramzi Saleh Saleem Alrutbi

E-mail: ramzrutbi91@gmail.com

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Abstract:

Partial correlations indicate that part of the age-dependent decrease in flow velocities can be attributed to a hemorheological decrement resulting in part from enhanced oxidative stress in the aged. A possible link with Alzheimer's pathology is suggested by the augmented hemorheological impairment resulting from in vitro incubation of red cells with amyloids. These results suggest that in aging, oxidative stress as well as amyloids may influence the fluid properties of blood, resulting in a potential decrement in blood flow and oxygen delivery to the brain. Intervention studies further demonstrate that altered hemorheological properties of blood can actually influence cognitive function. The relationships shown to exist between hemorheology, blood flow, amyloids, oxidative stress, and cognitive function suggest that these factors may be one of the mechanisms operating in the complex etiology of Alzheimer's disease.

Keywords: Cognitive Function, Hemodynamics, Geriatric.

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Introduction:

Cognition is critical for functional independence as people age, including whether someone can live independently, manage finances, take medications correctly, and drive safely. In addition, intact cognition is vital for humans to communicate effectively, including processing and integrating sensory information and responding appropriately to others. Cognitive abilities often decline with age. It is important to understand what types of changes in cognition are expected as a part of normal aging and what type of changes might suggest the onset of a brain disease(**1).**

It is imperative to understand the effects of age on cognition because of the rapidly increasing number of adults over the age of 65 and the increasing prevalence of age-

associated neurodegenerative dementias. Over the past century, the life span for both men and woman has increased dramatically. For example, in 1910 the life expectancy of a man was 48 years and a woman was 52 years. In 2010, this has increased to 76 years for men and 81 for women. The number of Americans over the age of 65 is projected to more than double over the next 40 years, increasing from 40 million in 2010 to 89 million in 2050. Because many more people are living longer, the number of people with age-associated neurodegenerative dementias also is increasing rapidly (**2).**

The Alzheimer's Association estimates that 5.2 million people in the United States had a clinical diagnosis of Alzheimer disease (AD) in 2014, and the number of people with a diagnosis of AD is projected to increase to 13.8 million people in 2050, unless effective preventative or treatment strategies are developed. Thus, it is vital to understand how age impacts cognition and what preventative or treatment strategies might preserve cognition into advanced age. Any approaches that could decrease the negative effects of age on cognition or decrease the risk of developing a neurodegenerative dementia would have a tremendous impact on the quality of life of millions of older adults in the United States(**3).**

Changes in Cognition with Normal Aging:

To appreciate how cognition changes with normal aging requires an understanding of some of the limitations that are inherent in studying cognition and aging. Studies of cognition across the life span are subject to several biases, some of which apply in general and some that are specific to study design. General biases include recruitment bias and misclassification bias. Recruiting subjects for any clinical research study may be biased by which subjects are willing to enroll (recruitment bias). For example, those who are too ill or have more limited social and financial support may find it hard to participate (**4).**

Recruitment bias tends to underestimate the degree of cognitive decline seen with aging because only the healthiest or most advantaged are included in the study. Misclassification bias is when a subject is misclassified in a research study, such as classifying a subject as normal when they are not. For example, by misclassifying a subject as normal when they actually have early signs and symptoms of a degenerative dementia, this subject's cognitive test scores would overestimate the degree of cognitive decline attributed to normal aging and add a misclassification bias to the study (**5).**

Study design biases include cohort bias, practice effect (learning) bias, and attrition (survival) bias. Cohort bias occurs in cross-sectional study designs that compare groups of subjects (cohorts) in specific age groups on their performance on cognitive tests. The cohort bias is the difference between groups that is not due to aging but is due to other differences, often unmeasured, between the age cohorts. For example, when comparing a cohort of subjects that were born in the 1990s to subjects born in the 1940s, the two cohorts might differ significantly in nutritional variables, childhood educational experiences, exposure to environmental toxins or social stressors, knowledge of new technology, and other unmeasured variables. These other factors may influence test

performance over and above normal cognitive aging (**6).**

Longitudinal studies examine how an individual person performs on cognitive tests over time to understand how aging affects cognition. One limitation of longitudinal studies is the practice effect (or learning) bias. By testing subjects on similar test batteries over time, there is the potential for improvement in test performance due to a practice effect. A second bias found in longitudinal studies is attrition or survival bias. If there is selective attrition of subjects over time, the remaining subjects' results may not be generalizable to other older adults (**7).**

For example, if a subgroup of patients selectively remains in the study (e.g., the healthiest or the best educated), their change in cognition may not accurately reflect the change in cognition with normal aging for many older adults. Both learning bias and attrition bias tend to underestimate the degree of cognitive decline seen with age. Despite these limitations in studying normal cognitive aging, there is research evidence of predictable and reproducible changes in cognition that occur with normal aging (**8).**

The most common terminology, used to describe which cognitive abilities change with age and which do not, divides cognitive abilities into crystallized abilities and fluid abilities. Crystallized abilities are the cumulative skills and memories that result from cognitive processing that occurred in the past, typically in the form of acquired knowledge. Tests of general knowledge (e.g., reading comprehension, math, science), historical information, and vocabulary would reflect crystallized abilities (**5).**

Fluid abilities require cognitive processing at the time of assessment and reflect manipulation and transformation of information to complete the test. Tests of fluid abilities require the subject to attend to one's environment and process new information quickly to solve problems. Multiple cross-sectional studies have shown that there is an improvement in crystallized abilities until approximately age 60 followed by a plateau until age 80, and there is steady decline in fluid abilities from age 20 to age 80. For example, there is a nearly linear decline in processing speed, a fluid ability, with a −0.02 standard deviation decline per year in one very large study (**5).**

Cognitive abilities can be divided into several specific cognitive domains including attention, memory, executive cognitive function, language, and visuospatial abilities. Each of these domains has measurable declines with age. For each of these domains, a subject must first perceive the stimulus, process the information, and then respond. Both sensory perception and processing speed decline with age, thus impacting test performance in many cognitive domains(**8).**

For example, auditory acuity begins to decline after age 30, and up to 70% of subjects age 80 have measurable hearing loss. Also, speech discrimination and sound localization decrease in advance age. In addition to these change in sensory perception, there is a clear decline in processing speed in advancing age with older adults performing these activities more slowly than younger adults. This slowing of processing speed causes worse test performance on many types of tasks that involve a timed response (**5).**

The most noticeable changes in attention that occur with age are declines in performance on complex attentional tasks such as selective or divided attention. Selective attention is the ability to focus on specific information in an environment while at the same time ignoring irrelevant information. Divided attention is the ability to focus on multiple tasks simultaneously, such as walking an obstacle course and answering questions. Normal subject performance declines progressively with age on these more complex attentional tasks. However, simple attention tasks such as digit span are maintained in normal subjects up to age 80 (**7).**

Some aspects of memory are stable with normal aging, but there are consistent declines in new learning abilities with increasing age and some decline in retrieval of newly learned material (**8)**

Immediate or "sensory memory" is stable with age, but tests that require subjects to exceed normal primary storage capacity (e.g., six to seven items) are more difficult for older adults. Historical memories for public events and autobiographical memories (episodic memory) are relatively stable with advanced age, but the accuracy of source memory (i.e., accurately knowing the source of the known information) declines with age, as does the level of detail of recalled episodic memories. New learning, as measured by delayed free recall, also declines with age. Learning is further compromised in older adults if the test requires mental manipulation of the material to be learned (working memory) or if subjects must perform more than one activity while learning (divided attention) (**6).**

Working memory requires active manipulation of material to be learned and declines with age. Retention of newly learned information is relatively stable with advancing age, but retrieval of information may require more cueing or a recognition format to remain stable in advanced age groups. Prospective memory, specifically remembering to perform intended action in the future (e.g., taking medication after breakfast), declines with age. Procedural memories, such as remembering how to play the piano or ride a bike, are preserved with age. Executive cognitive function involves decision making, problem solving, planning and sequencing of responses, and multitasking. Each of these areas of executive cognitive function declines with advancing age (**8).**

Executive cognitive function is particularly important for novel tasks for which a set of habitual responses is not necessarily the most appropriate response and depends critically on the prefrontal cortex. Performance on tests that are novel, complex, or timed steadily declines with advancing age, as does performance on tests that require inhibiting some responses but not others or involve distinguishing between relevant and irrelevant information. In addition, concept formation, abstraction, and mental flexibility decline with age, especially in subjects older than age 70 (**8).**

Speech and language function remains largely intact with advancing age. Vocabulary, verbal reasoning, and speech comprehension in normal conversation all remain stable into advanced age. Speech comprehension in the setting of background noise and ambiguous speech content declines with age. Speech comprehension

involves both the peripheral nervous system's sensitivity for perception and the central nervous system's speech-specific cognitive abilities **(7).**

These central nervous system cognitive abilities are especially important under less favorable listening conditions and are sensitive to changes with age. Recent work suggests that aging-related changes in left frontal lobe structures correlate with performance on a speech-in-noise test. Verbal fluency, verbal retrieval, and some confrontational naming tasks show some decline with age. Critchley observed that in advanced age, older adults were less verbose, more repetitive, and less specific in word choice in spontaneous speech when compared with young adults **(8).**

There are age-related declines in aspects of visuospatial processing and constructional praxis. Visual recognition of objects, shapes, gestures, and conventional signs remains stable into advanced age. However, visuoperceptual judgment and ability to perceive spatial orientation decline with age. A person's ability to copy a simple figure is not affected by age, but ability to copy a complex design (e.g., Rey figure) declines with age. On standard IQ measures such as block design and object assembly, much of the declines with age are due to time, but when time is factored out, there are still declines in test performance with increasing age. On free drawing tasks, pictures drawn by older adults become more simplified and less articulated with age **(6).**

Age-Related Changes in Brain Structure and Function:

The size of the brain decreases with age. The brain is often divided into gray matter and white matter based on the brain's appearance at autopsy. *Gray matter* is used to describe the cerebral and cerebellar cortex and subcortical nuclei, each of which contains a predominance of cell bodies and dendrites. *White matter* refers to regions of the brain with a predominance of myelinated axons that connect gray matter structures. Not all brain areas develop atrophy equally with aging, but both gray and white matter regions are affected with aging **(7).**

Gray matter volume loss is most prominent in the prefrontal cortex. The temporal lobes, especially the medial temporal lobe, which includes the hippocampus, also show moderate declines in volume with aging. White matter volumes decline with age also. The greatest white matter volume losses are seen in the frontal lobe white matter and in major white matter tracts such as the corpus callosum. In addition to age-related decreases in volume of the white matter, there is evidence of a decline in white matter tract integrity with age, using MRI diffusion tensor imaging **(8).**

It has been assumed that gray matter volume loss was due to neuronal loss, but with improvements in neuron-counting techniques, it is now clear that this is not the case. Many studies demonstrate that loss of neurons during normal aging is restricted to specific regions of the nervous system and that this loss is no more than 10% of neurons found in young adults. Cortical neuronal loss is most notable in the dorsal lateral prefrontal cortex and hippocampus, and greater subcortical neuronal loss can be seen in the substantia nigra and cerebellum**(8).**

Age-related neurodegenerative diseases such as AD are associated with much greater loss of neurons, especially in the hippocampus and entorhinal cortex. In

normal aging, a substantial number of neurons change in structure but do not die. These aging-related structural changes to neurons include a decrease in the number and length of dendrites, loss of dendritic spines, a decrease in the number of axons, an increase in axons with segmental demyelination, and a significant loss of synapses. Synaptic loss is a key structural marker of aging in the nervous system (**7).**

The number of neuronal synapses can now be measured using immunohistochemistry techniques that label presynaptic proteins, such as synaptophysin. Using synaptophysin antibodies to quantify presynaptic terminals in the superior, prefrontal gyrus, a steady decline in synaptic number can be seen across the life span. Results from dementia research suggest that symptomatic dementia occurs when there is a 40% or greater loss of neocortical synapses as compared with normal adults(**8).**

Using the rate of change in cortical synapses seen with normal aging and the 40% synaptic loss threshold, Terry and Katzman predicted that dementia due to aging (senility) would occur at approximately age 130 without requiring the development of a disease state such as AD. They also discussed the concept of cognitive reserve in terms of cortical synaptic density and discussed how synaptic reserve, aging, and the development of a neurodegenerative disease could all impact when a person would cross the symptomatic threshold of 40% loss of cortical synapses and develop signs and symptoms of dementia. For example, those with a synaptic density deficiency at birth (e.g., low synaptic reserve due to neonatal hypoxic brain injury) would cross the 40% synaptic threshold earlier in life with the same rate of synaptic loss with aging (**8).**

Similarly, the development of a neurodegenerative disease such as AD would accelerate the rate of synaptic loss. The age of dementia symptom onset would be determined by a combination of how close the person was to the 40% synaptic threshold at the time of disease onset and how quickly synapses were lost due to disease. Alternatively, if there was a preventative lifestyle or treatment that slowed the rate of cortical synaptic loss caused by aging, then the 40% synaptic threshold would be reached later in life and this person would have greater synaptic reserve to compensate for degenerative disease-associated synaptic loss (**7).**

Age-related changes in the structure and function of synapses and changes in neuronal networks correlate with cognitive changes with aging. Morrison and Baxter reviewed the aging changes that occur in the cortical synapse in the dorsal lateral prefrontal cortex, an area important in working memory and executive function, and the hippocampus, an area vital for learning and memory. They summarized the morphological and functional changes that occur at these synapses and how these changes may correlate with changes in cognitive function (**5).**

For example, in the dorsal lateral prefrontal cortex, there is a 46% loss of one subtype of cortical neuron dendritic spines (i.e., thin spines). These spines are the most plastic spines and their loss causes a loss of dynamic plasticity in the ever-changing circuits that are important for cognitive flexibility, working memory, and executive cognitive function (**5).**

Interestingly, there is relative stability of a second type of dendritic spine (i.e., mushroom spine) in the dorsal lateral prefrontal cortex, which mediates more stable circuits that may be related to maintenance of crystallized cognitive abilities (i.e., experiential expertise). Resting state functional MRI imaging (rs-fMRI) can identify functional connectivity across distinct brain regions. A series of intrinsic connectivity networks have been identified, including networks important for memory, organization, and coordination of neuronal activity, priming of the brain for coordinated responses, and the default mode network (DMN), which is active in the absence of a task. The DMN is thought to be important for memory consolidation (**8).**

Connectivity and network integrity appear to decrease in normal aging. In neurodegenerative diseases, such as AD, these declines and disruptions are accelerated, especially in the DMN, and can bias rs-fMRI studies of normal aging that include subjects with preclinical AD. Correlation of structural changes in the brain and measured age-related, cognitive changes have been modest and at times inconsistent, but inclusion of functional measures such as blood flow, glucose metabolism, and rs-fMRI or the combination of functional and structural measures can provide stronger correlations(**6).**

Age-Associated Diseases and Cognition:

A variety of factors can cause cumulative damage to the brain with age and produce cognitive impairments. These factors include damage to the brain due to cerebral ischemia, head trauma, toxins such as alcohol, excess stress hormones, or the development of a degenerative dementia such as AD. Degenerative dementias are the most common cause of significant late-life cognitive decline, but a combination of factors is common. Community-based autopsy series of patients who died with dementia found that the most common cause of dementia was AD, followed by vascular dementia, and then dementia with Lewy bodies. However, mixed dementia or dementia caused by more than one pathology was very common (**6).**

These same pathologic changes are very common in older adults without dementia. In a large clinical-pathologic study of older adults without dementia combining participants from the Rush Memory and Aging Project and the Religious Orders Study, 100% had neurofibrillary tangles, 82% had amyloid plaques, 29% had macroscopic infarcts, 25% microscopic infarcts, and 6% had neocortical Lewy bodies. Because of the very common overlap of disease-associated pathology and cognitive decline in the elderly population, it is difficult to separate disease-related declines in cognition from those due the normal aging(**8).**

A recent larger study from the same longitudinal studies found that faster rates of cognitive decline were associated with AD pathology, macroscopic infarcts, and neocortical Lewy bodies, but the combination of all of these pathologies explained only 41% of the variation in rate of decline in this sample of older adults without dementia. Thus, these late-life diseases cause an acceleration of cognitive decline that results in the development of dementia in many patients, but some older adults without dementia do have cognitive

decline not caused by these pathologic changes (**7).**

AD is the most common cause of cognitive decline in older adults. The prevalence of clinically diagnosed AD increases exponentially with age. At age 65, less than 5% of the population has a clinical diagnosis of AD, but this number increases to more than 40% beyond age 85. For patients who develop AD, most first demonstrate a subtle decline in memory and new learning, followed by mild changes in executive cognitive function and later changes in language and visuospatial processing. Many of these changes in cognition are similar to normal cognitive aging changes, but differ by severity. The onset of cognitive decline is subtle and hard to determine. Progression is gradual and may be more apparent to family members than the patient(**7).**

Clinically, most patients first develop mild cognitive impairment (MCI), which is defined as a syndrome of cognitive complaints, measureable mild declines in cognition, but no change in functional abilities, including instrumental activities of daily living. MCI can involve one or more cognitive domains, but memory domain-only MCI (i.e., amnestic MCI) is seen most commonly in patients who go on to develop AD. If cognitive impairments continue to progress and the patient develops evidence of functional impairment caused by these cognitive impairments, then he or she would be diagnosed as having dementia. If the patient meets the clinical criteria for AD, then he or she would be diagnosed with probable AD. Longitudinal studies suggest that the conversion rate from amnestic MCI to probable AD is ~15% per year (**8).**

PET imaging of glucose metabolism uses fluorodeoxyglucose (FDG-PET) as a marker of neuronal activity and neurodegeneration. Glucose metabolism, as detected by FDG-PET, declines in the posterior cingulate gyrus and the association cortices of the temporal and parietal lobes closer to the time of measureable cognitive decline. Additional markers of neurodegeneration include volumetric MRI measurements of the hippocampus and measurements of cerebrospinal fluid levels of the protein tau. These biomarkers begin to show changes before very mild cognitive symptoms appear and can be measured. New diagnostic classifications for AD have recently been proposed that incorporate these biomarkers. This classification system includes a determination of whether there is evidence of amyloid deposition, neurodegeneration, or both and whether cognition and function are normal or abnormal (**7).**

Patients with stage 1 disease have cerebral amyloidosis only; those with stage 2 disease have amyloidosis plus neurodegeneration but no cognitive decline; those with stage 3 disease have amyloidosis, neurodegeneration, subtle cognitive decline, but no functional decline; and those with stage 4 disease have amyloidosis and neurodegeneration, with measurable cognitive and functional decline. The availability of these new biomarkers and the new classification system has been helpful to define preclinical AD for prevention trials; individuals with preclinical AD have evidence of amyloid deposition on amyloid PET imaging, but normal cognition and function (i.e., stage 1 and 2 AD), and AD biomarkers predict incident cognitive

impairment in cognitively normal subjects followed longitudinally (**7).**

Modifying Age and Disease Effects on Cognition:

With aging, there is a dynamic interplay between factors that leads to neurodegeneration and cognitive impairment and factors that lead to neuroplasticity and improved cognitive function. A growing body of research uses automated, high-resolution MRI measurements of hippocampal size as a practical and reliable measure of this dynamic balance. Hippocampal size is associated with memory and cognitive function in normal individuals, and atrophy of the hippocampus is associated with dementia due to AD and conversion from amnestic MCI to clinical AD (**7).**

Recently, growing evidence has indicated that a variety of factors are associated with decreased hippocampal size including diabetes mellitus, hypertension, obesity, hypoxic brain injury, obstructive sleep apnea, clinical depression, bipolar disorder, alcoholism, and head trauma. Importantly, the hippocampus possesses a high capacity for neuroplasticity. In the past several years, a growing number of interventional studies have looked at the ability of intervention to slow the rate of hippocampal atrophy or reverse such atrophy caused by degenerative, cerebrovascular, metabolic, or traumatic causes (**6).**

A variety of cellular mechanisms of neurodegeneration and neuroplasticity have been proposed and are being actively investigated as to how they may mediate neuronal health and hippocampal size and ultimately cognitive function. Microvascular ischemia, inflammation, oxidative stress, excitotoxicity, and apoptosis are common mechanism of neurodegeneration, and there are multiple common signaling pathways that are important for neuroplasticity including pathways important for neuronal differentiation, plasticity, and survival (**6).**

Ultimately, decreasing the presence or impact of neurodegeneration and increasing the activity of signaling pathways important for neuroplasticity could decrease hippocampal atrophy and cognitive decline that is so common with aging. There is emerging evidence that healthy lifestyle choices improve the dynamic balance toward neuroplasticity and away from neurodegeneration including eating a healthy diet; avoiding excessive alcohol consumption; exercising regularly; participating in cognitive stimulating activities; managing emotional stress, which might include meditation; and managing medical problems such as hypertension, diabetes, depression, and obstructive sleep apnea (**7).**

Observational studies and preliminary clinical trials have raised the possibility that physical exercise and cognitive training or stimulation may improve cognitive function in older adults with normal cognition and potentially in those with AD and other forms of dementia. Previous reviews have summarized the literature concerning physical activity, enhanced fitness, and cognitive function in older adults without cognitive impairment and have concluded that the preponderance of evidence suggests that physical activity is beneficial for cognitive function in the elderly population, but that a majority of the evidence is based

on studies with potential methodological problems and moderate risk of bias (**7).**

These studies have not determined which types of exercise are most beneficial in general or on specific types of cognitive function. A large, well-controlled study of older adults with normal cognition examined the impact of cognitive training on cognitive abilities and functional outcomes over 5 years of follow-up. Cognitive training resulted in improved cognitive abilities specific to the abilities trained, and these improvements persisted for 5 years after the initial intervention. The subgroup that received reasoning training had less functional decline at 5 years, as measured by self-reported ability to perform instrumental activities of daily living (**5).**

Similar to older adults with normal cognition, physical activity and cognitive stimulation may benefit those at risk for AD or those that have a diagnosis of dementia. A recent observational study found that normal middle-aged subjects who were more physically active demonstrated less AD biomarker abnormalities than those who were physically inactive, including less amyloid burden on amyloid PET imaging and less neurodegeneration based on MRI measurements of hippocampal volume and FDG-PET measurements of glucose metabolism (**7)**.

Haemodynamic effects of vascular aging:

However, as arterial stiffness is a characteristic of vascular aging based on morphological changes in the arterial wall there is also a need to understand its haemodynamic consequence. More specifically, what are the consequences of normal aging on blood pressure and pulse rate regulation in western populations and what is outside this normal range? A starting point is to try to list different characteristics of haemodynamic aging and to try to understand the association with underlying morphological changes in the arteries (**9).**

Arterial stiffness as a core characteristic of age-related haemodynamic changes:

There are, however, also other features of haemodynamic aging 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(**10).**

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*. 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 risk mechanisms 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 (**11).**

In a corresponding way it has been reported that a decrease in heart rate variability (HRV) is a marker of aging and increased cardiovascular risk, but also associated with increased arterial stiffness, for example in patients with type 1 diabetes(**12).**

It is conceivable to think that more widespread changes in innervation and the autonomic nervous system could contribute to the aging of the neural system and thus linked to vascular aging and decreased baroreceptor function as well as imbalance between sympathetic and parasympathetic activity. One recent study tested the relationship between direct measures of sympathetic traffic and PWV in healthy humans (**12).**

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 and MSNA 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, explaining 39 and 25% of its variance, respectively (**13).**

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. A cross-talk between the sympathetic nervous system and the renin-angiotensin system takes place in the arterial wall. The effects of this interaction will further decrease elasticity and promote vascular aging (**14).**

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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 role 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 (**13).**

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Cardiac-arterial coupling influenced by arterial stiffness:

Finally, it is self-evident that haemodynamic changes associated with aging 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. There is thus a cross-talk between cardiac function and the general circulation in the arterial tree. With increasing stiffening of the proximal thoracic aorta the reflected wave from the periphery back to the central circulation and the heart can no longer be accommodated (**10).**

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 (**13).**

This is therefore a hemodynamic 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 aging continuum by O'Rourke, Safar and Dzau (**15).**

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