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# Évaluation du lien entre la viscosité pariétale artérielle carotidienne et les troubles neurocognitifs majeurs d'origine vasculaire ou lien avec une maladie d'Alzheimer. Étude VISCOG

Gabrielle Noël

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**THESE POUR LE  
DOCTORAT EN MEDECINE**

(Diplôme d'Etat)

Par

**NOEL Gabrielle**

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**Evaluation of the link between carotid arterial  
wall viscosity and vascular dementia or  
Alzheimer's disease (VISCOG)**

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## II.ABBREVIATIONS

<b><math>\Delta</math>LCSA:</b>	Arterial cross-sectional area changes
<b><math>\Delta</math>P:</b>	Blood pressure changes
<b>AD:</b>	Alzheimer's disease
<b>AIx:</b>	Augmentation index
<b>AIx 75:</b>	Augmentation index normalized to the heart rate at 75 beats/minutes
<b>AP:</b>	Augmentation pressure
<b>AWV:</b>	Arterial wall viscosity
<b>BADL:</b>	Basic activity of daily living
<b>BMI:</b>	Body mass index
<b>CCA:</b>	Common carotid artery
<b>cPP:</b>	Central pulse pressure
<b>CPP:</b>	Committee for the protection of persons
<b>CV:</b>	Coefficient of variation
<b>DBP:</b>	Diastolic blood pressure
<b>DC:</b>	Distensibility
<b>DSM-V:</b>	Diagnostic and statistical manual of mental disorders V
<b>ECM:</b>	Extracellular matrix
<b>Einc:</b>	Incremental Young's elastic modulus
<b>FDG PET:</b>	Fluorodeoxyglucose positron emission tomography
<b>GDS:</b>	Geriatric depression scale
<b>GFR:</b>	Glomerular filtration rate
<b>IADL:</b>	Instrumental activity of daily living
<b>IMT:</b>	Intima-media thickness
<b>HR:</b>	Heart rate
<b>LCC:</b>	Lin's correlation coefficient
<b>LCSAd:</b>	Diastolic lumen area
<b>MBP:</b>	Mean blood pressure
<b>MMSe:</b>	Mini mental state examination
<b>MRI:</b>	Magnetic resonance imaging
<b>PET:</b>	Positron emission tomography
<b>P-LCSA:</b>	Pressure lumen cross sectional area
<b>PP:</b>	Pulse pressure
<b>pPP:</b>	Peripheral pulse pressure
<b>PWV:</b>	Pulse wave velocity

<b>QAPPA:</b>	Physical activity questionnaire for the elderly
<b>ROI:</b>	Region of interest
<b>SBP:</b>	Systolic blood pressure
<b>SMC:</b>	Smooth muscle cells
<b>VaD:</b>	Vascular dementia
<b>WCSA:</b>	Wall cross-sectional area
<b>W<sub>E</sub>:</b>	Stored elastic energy
<b>WHO:</b>	World health organization
<b>W<sub>V</sub>:</b>	Dissipated viscous energy, absolute viscosity
<b>W<sub>V</sub>/W<sub>E</sub>:</b>	Relative viscosity



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**Figure 1:** Pressure-diameter curves (left) are overlaid during the systolic phase (blue lines), then curves split with a higher diameter (plain red line) at each level of pressure (dashed red line) during diastolic phase. The pressure-diameter relationship results in a hysteresis loop (right).

**Figure 2:** Simultaneous acquisition of ultrasound 1 cm upstream of the carotid bifurcation, contralateral carotid tonometry (red line) and ECG signal (green line) on the Vevo 3100®.

**Figure 3:** Manual definition of the desired area of interest represented by the red square (ROI). Automatic detection of the inter adventitial diameter, including the IMT, delimited by the two red lines.

**Figure 4:** Manual definition of the desired area of interest represented by the red rectangle (ROI). Automatic detection of the intima-media thickness delimited by the double lines surrounding the IMT.

**Figure 5:** Asynchrony of pressure curves in mmHg (blue) and LCSA curves in mm<sup>2</sup> (red) as a function of time over the entire acquisition (in ms) (A), over a pressure and LCSA cycle (B) and the resulting P-LCSA loop (C).

**Figure 6:** Curves of pressure in mmHg (blue) and LCSA in mm<sup>2</sup> (red) as a function of time over the entire acquisition (in ms) (A), over a pressure and LCSA cycle (B) and the resulting P-LCSA loop after the synchronization of the wave feet (C).

**Figure 7:** Schematic representation of the measurement of hysteresis loop and elastic energy stored.

**Figure 8:** Measurement of carotid-to-femoral PWV with the foot-to-foot method.

**Figure 9:** Pressure waveform analysis.

**Figure 10:** Flow-chart of the study.

**Figure 11:** Comparison of  $W_V/W_E$  between patients with or without dementia. Comparisons were performed with the Kruskal-Wallis rank sum test ( $p=0.015$ ).  $W_V/W_E$ : relative viscosity.

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**Table 1:** Baseline characteristics of the population.

**Table 2:** Geriatric characteristics of patients according to the group (dementia or no dementia).

**Table 3:** Cardiovascular characteristics of patients according to the group (dementia or no dementia).

**Table 4:** AWW of patients according to the group (dementia or no dementia).

## V. ABSTRACT

**Background:** Aging is characterized by arterial stiffening of large arteries, which is associated with vascular dementia (VaD) and Alzheimer disease (AD). However, arteries are not only elastic but viscoelastic. The arterial wall viscosity (AWV) has been less studied. AWV results in a hysteretic pressure-area relationship whose area corresponds to the energy dissipated in viscous work ( $W_V$ ) during each cardiac beat. No study has evaluated the association between AWV and VaD or AD.

**Objective:** The primary objective of this study was to compare the AWV and the arterial stiffness of CCA of patients with dementia (AD or VaD) to patients without dementia. The final objective of VISCOG study will be to compare the AWV between 3 groups: VaD, AD and absence of dementia.

**Methods:** In this prospective, cross-sectional, monocentric study, 43 elderly patients over 70 years with dementia (n=25) or no dementia (n=18) were included. The hysteresis loop of the pressure-diameter area relationship was obtained using carotid tonometry and contralateral high resolution carotid ultrasound. AWV was measured by planimetry and expressed as absolute value ( $W_V$ ) or as a percentage of the elastic energy stored within the arterial wall during the cycle ( $W_V/W_E$ ). Arterial stiffness was assessed noninvasively by the carotid-to-femoral PWV (c-f PWV).

**Results:** The median age of patients was 80 [76.1 - 85.5] years old (n = 27 women). The median MMSe was 20 [16 - 23] in the group of patients with dementia, and 28 [26 - 28] in patients without dementia. There was no difference between groups concerning major cardiovascular comorbidities or baseline blood pressure values.  $W_V$  and  $W_E$  were similar in the both groups ( $W_V$ : 38 mmHg.mm<sup>2</sup> [25 - 56] vs. 31 mmHg.mm<sup>2</sup> [19 - 45], p=0.3 et  $W_E$ : 137 mmHg.mm<sup>2</sup> [108 - 203] vs. 156 mmHg.mm<sup>2</sup> [106 - 215], p=0.9). However, the relative viscosity ( $W_V/W_E$ ) was higher in patients with dementia ( $W_V/W_E$ : 25.2% [21.9- 28.7] vs. 19.9% [17.3 – 25.5], p=0.015). Arterial stiffness was similar between both groups.

**Conclusion:** The preliminary results of this study suggest for the first time an association between carotid AWV and dementia.

**Keywords:** aging, arterial wall viscosity, arterial stiffness, dementia.

## **VI.INTRODUCTION**

### **1. Dementia**

Dementia is a common neurological disorder and the main cause of disability in old people. Fifty-five million people have dementia worldwide and there are 10 million new cases per year. As the proportion of old people increased, the prevalence of dementia is expected to rise to 139 million in 2050 (WHO, 2022). Alzheimer's disease (AD) and vascular dementia (VaD) are the most frequent subtypes of dementia in old people.

AD may contribute to 60-70% of dementia cases. The diagnosis of AD is histological by the demonstration of neurofibrillary degeneration and amyloid plaques, but diagnosis criteria based on clinical data and biomarkers are used in clinical practice and in research studies (McKhann and al. 2011; Dubois and al. 2014). The course of AD begins with the onset of mild cognitive impairment mainly expressed by inability to encode and store new memories. At this time, the autonomy for most activities of daily life is retained. Subsequently, in addition to memory disorders, there is an impairment of other cognitive functions with consequences on autonomy, characterizing major neurocognitive disorders or dementia in mild to moderate stages. The most advanced phase of the disease is characterized by a complete loss of autonomy, the occurrence of psychological and behavioural disorders and evolving until death. There are three groups of biomarkers based on the nature of the pathologic process: biomarkers of A $\beta$  plaques (cortical amyloid PET ligand binding or low cerebrospinal fluid AB42), biomarkers of fibrillar tau (elevated cerebrospinal fluid phosphorylated tau and cortical tau PET ligand binding) and biomarkers of neurodegeneration or neuronal injury (cerebrospinal T-tau, FDG PET hypometabolism and hippocampic atrophy on MRI). In the geriatric population (age over 80), the usefulness of these biomarkers is uncertain because of their lower specificity compared to young subjects (Molin and Rockwood 2016).

The diagnosis of VaD is complex due to the varied clinical presentation and multiple causes of this disease. In the DSM-V, VaD is defined by a mild or severe neurocognitive impairment temporarily related to one or more cerebrovascular events or by a cognitive impairment mainly focused on complex attention or frontal executive functions. The cerebrovascular disease, defined on disease history, physical examination, and/or neuroimaging, should be sufficient to explain the neurocognitive disorders and cannot be better explained by another disease or lesion of the central nervous system. Diagnosis scores based on clinical and radiological criteria has been proposed by the National Institute of Neurological Disorders and Stroke and Association International for Research and Education in Neuroscience (Román and al. 1993). They are based on the demonstration of dementia with impairment of episodic memory and of at least two other cognitive domains, a cardiovascular disease demonstrated by either history or clinical examination and typical brain imaging, CT or MRI. In addition to clinical evidence for cardiovascular disease, a temporal relationship between the dementia and stroke within the last 3 months or a stepwise deterioration in cognitive functions are needed.

Epidemiological and clinical data suggest a link between AD and vascular lesions of the brain (Casserly and Topol 2004). Vascular amyloid angiopathy is the most common vascular lesion reported in AD, present in almost all AD cases, and apolipoprotein E4 is a strong factor in its development (Premkumar and al. 1996). The cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, atherosclerosis and cerebrovascular disease and smoking could cause localised or global hypoperfusion that may lead to AD pathology, white-matter lesions or both (Gorelick and al. 2011). Thus, prevention of AD is becoming a major public health challenge as well as the identification of modifiable cardiovascular risk factors (WHO 2022).

## **2. Arterial stiffness**

### **a. Arterial stiffness and aging**

Vascular aging is responsible for major changes in the structure and the function of vessel. It is characterized by vascular remodelling including luminal dilation, thickening of the intimal and medial layers with cellular and extracellular matrix (ECM) reorganization, increased arterial stiffness and endothelial dysfunction. Indeed, vascular aging is characterized by elastin fragmentation, an increase in proportion of collagen and glycation of ECM proteins reducing collagenolysis and promoting the appearance of “cross-links” in collagen. Aging leads to changes in the vascular wall through inflammatory phenomena favoured by the increase in oxidative stress with the production of free radicals and amyloid deposits modifying its properties (Fritze and al. 2012; Sell and Monnier 2012). Furthermore, vascular remodelling is favoured by proliferation, migration of the media to the intima (Spinetti and al. 2004) and modification of the functional properties of smooth muscle cells (SMC), the latter willingly passing from a pro-contractile phenotype towards a pro-secreting, pro-inflammatory and pro-calcifying phenotype (Lacolley and al. 2017). Finally, aging is associated with endothelial dysfunction linked to a decrease in the main relaxing factors (Vanhoutte and al. 2017) and an increase in vasoconstrictor factors (Heymes and al. 2000).

Stiffness of the large arteries is the main phenotype of arterial aging and is responsible for reduced distensibility and an amplification of arterial wave reflection. The increase in large artery stiffness is a frequent condition with aging and is accelerated with vascular disease (O’Brien and al. 2003). The non-invasive gold standard measurement of aortic stiffness is the carotid-to-femoral pulse wave velocity (c-f PWV) which consists of measuring the time necessary for the pressure wave generated by myocardial contraction to travel through an arterial segment of known length (Laurent and al. 2006). PWV is considered an early phenotype of vascular damage and a potential prognosis factor in assessing cardiovascular risk (Laurent and al. 2001).

Vascular echo-tracking systems coupled with the measurement of local pressure by a tonometer, allow a more localized assessment of the stiffness of the large arteries such as the common carotid artery (CCA). The increase in arterial stiffness at the level of the large arteries have consequences on the arterial physiology but also on the function of the heart and peripheral organs. Indeed, the decrease in the elastic properties of the conductance arteries during aging alters their ability to damp the pulsatility of the blood flow (Benetos and al. 2012) and leads to an increase in the pulsatility transmitted to the peripheral organs.

#### **b. Arterial stiffness and dementia**

A link between arterial stiffness and AD or VaD is suggested. Indeed, some studies showed a positive correlation between a high PWV in an older population with AD or VaD compared to those without dementia (Hanon and al. 2005). Several studies have shown that a high PWV increases the risk of transition from mild cognitive impairment to dementia (Rouch and al. 2018) or from no dementia to dementia (AD or VaD) (Pase and al. 2016).

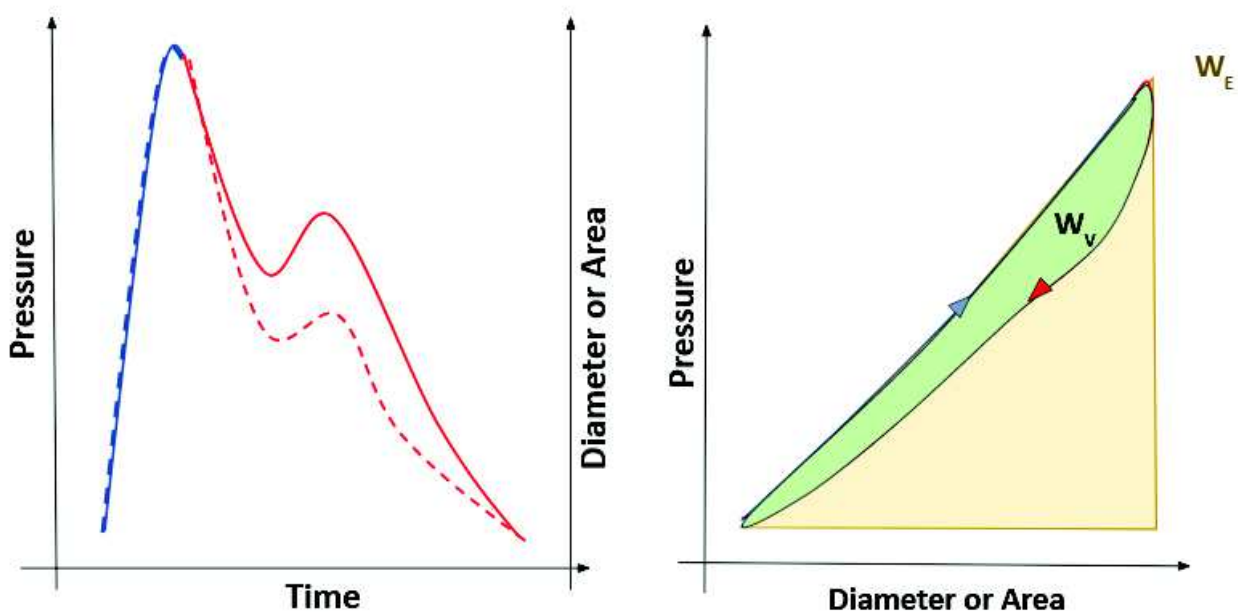
Moreover, a high aortic stiffness is associated with a more important decline in cognitive functions (Benetos and al. 2012) including the occurrence of memory disorders. Indeed, in patients with subjective memory complaint, an increased PWV is a strong predictor of later cognitive decline (Scuteri and al. 2007).

In addition, previous studies found a correlation between an increased PWV and markers of small vessel damages on MRI (leukoaraiosis, lacunae and microhaemorrhages) in asymptomatic old subjects (Mitchell and al. 2011). These results were independent from age, gender, and other cardiovascular risk factors in hypertensive patients (Henskens and al. 2008) but also in non-hypertensive patients (Tsao and al. 2013). Increase in arterial pulsatility transmitted to the small cerebral vessels could explain these results by promoting remodelling of the vessels and leading to these microvascular lesions. In addition, these microtrauma promote endothelial dysfunction (Kearney-Schwartz and al. 2009), the increase in oxidative stress and the production of free radicals. Finally, arterial stiffness could also alter the permeability of the cerebrovascular barrier and promote the accumulation of beta-amyloid proteins in the brain (Hughes and al. 2014).

### 3. Arterial wall viscosity

#### a. Definition

The mechanical behaviour of conductance arteries is viscoelastic. While arterial stiffness and therefore the elastic component of this behaviour has been widely studied, viscous component has been less investigated. The elasticity of the arterial wall allows the diameter to increase proportionally to the arterial pressure during systolic phase. The viscous component induces a delay in the restitution of the diameter resulting in a larger diameter at each level of pressure during diastolic phase. This leads to a shift between the systolic and diastolic curves of the pressure-diameter relationship, resulting in a hysteresis loop (Figure 1).



**Figure 1:** Pressure-diameter curves (left) are overlaid during the systolic phase (blue lines), then curves split with a higher diameter (plain red line) at each level of pressure (dashed red line) during diastolic phase. The pressure-diameter relationship results in a hysteresis loop (right).  $W_V$ : dissipated viscous energy, absolute viscosity;  $W_E$ : stored elastic energy;  $W_V/W_E$ : relative viscosity.

In a thermodynamic point of view, the energy stored within the arterial wall during the loading phase, is not fully restored during the unloading phase at each cardiac cycle. The AWW is responsible for this dissipation of energy. The hysteresis loop resulting from the shift between the loading and the unloading phases of the pressure-lumen cross-sectional area (P-LCSA) curves, corresponds to the viscous energy dissipated ( $W_V$ ), whereas the area under the loading curve reflects the elastic energy stored ( $W_E$ ). The AWW can therefore be measured by planimetry and expressed either as an absolute value of  $W_V$  or relative to the energy stored ( $W_V/W_E$ ) (Boutouyrie and al. 1997; Roca and al. 2018, 2019).

Physiologically, this loss of energy is low. Its increase could be accompanied by an excessive dissipation of energy leading to an increase in cardiac work, itself responsible for an alteration of the cardio-vascular coupling (Boutouyrie and al. 1997; Armentano and al. 1998). Conversely, its reduction could lead to default of damping and thus could cause damages to peripheral organs by the excessive transmission of pulsatile energy to the periphery.

#### **b. Factors modifying the properties of AWV**

The factors modifying the viscous component of the arteries have not yet been studied in detail. Arterial loading conditions such as wall stress (pressure exerted per unit area of the arterial wall), pulse pressure (PP) and heart rate (HR) seem to modify AWV. Indeed, indirect results in hypertensive subjects showed an increase in absolute viscosity secondary to an increase in midwall stress (Armentano and al. 2006). In addition, work from our laboratory found a proportional increase in  $W_V$  and  $W_E$  during the decrease in HR induced by a bradycardic agent in young healthy subjects, resulting in a stability of  $W_V/W_E$ . However, this adaptative response of the arterial wall to change in loading conditions is lost with aging, resulting in an increase in  $W_V/W_E$  (Roca and al. 2022).

The intrinsic properties of the components of the vascular wall also contribute to the AVW. Indeed, changes in the composition of elastin, collagen or ECM proteoglycans and their interactions are associated with changes in AWV (Wang and al. 2015). Several in-vitro studies have suggested that SMCs are one of the main determinants of arterial viscous component (Dobrin 1978). In humans, increased intima-media thickness (IMT) in hypertensive patients is associated with increased carotid AWV (Armentano and al. 1998) while ACE inhibitors reduce AWV through anti-remodelling effects (Armentano and al. 2006). Finally, we showed, in humans, the role of endothelial vasorelaxing factors (endothelial nitric oxide and epoxyeicosatrienoic acids) and smooth muscle tone in basal regulation of radial AWV (Roca and al. 2018).

#### **c. Changes in AWV during aging and pathological conditions**

The physiological effects of aging on AWV are poorly understood and some results are controversial. Some studies suggest an increase in AWV with aging (Kawano and al. 2013) while others showed a drop in absolute viscosity (Giannattasio and al. 2008). These contradictory results can be explained by differences in the methodology used for evaluating AWV, but also by differences in loading conditions in these studies. Recent results obtained in our laboratory and taking into account loading conditions of the artery, found a drop in carotid AWV with aging (Roca and al. 2022). These results are similar to those found by another team (Giudici and al. 2021).



$W_E$  and  $W_V$  increase with hypertension resulting in a stable relative viscosity ( $W_V/W_E$ ) and suggesting that the increase in AWW is an adaptative process to the increase in loading conditions (Armentano and al. 2006; Roca and al. 2019). The increase in absolute viscosity could be explained by the arterial hypertrophy, secondary to the hypertrophy and the increase in the number of SMCs during hypertension (Armentano and al. 1998). However, endothelial dysfunction observed during hypertension results in the loss of the regulation of AWW (Roca and al. 2019).

In diabetic subjects, a study has suggested the absence of change in AWW (Giudici and al. 2021) contrary to preliminary results in our laboratory suggesting an increase in  $W_V$  and  $W_V/W_E$  at the level of the CCA (DIABEETs Study – preliminary data).

No study assessed the impact of AWW on hypertension target organs such as the kidney or the brain. It is speculated that a low AWW could lead to less energy dissipation within the arterial wall, favours the transmission of arterial pulsatility and thus damages the microcirculation of the brain (Armentano and al. 2006, 2007).

#### **4. Study objectives**

The link between AWW and dementia (AD or VaD) or the severity of dementia is unknown. The main objective of our study is to compare the AWW of the CCA between patients with dementia (AD or VaD) and patients with memory complaint but without objective impairment.

The secondary objective is to compare the arterial stiffness of the CCA between patients with dementia (AD or VaD) and patients with memory complaint but without objective impairment.

The final objective of the study will be to compare AWW of the CCA between the 3 groups: VaD, AD and absence of dementia.

## **VII.METHODS**

### **1. Study population**

The VISCOG study is a prospective, cross-sectional and monocentric study carried out at the Rouen University Hospital since February 2022 and scheduled to end in February 2024. It includes patients over 70 years old followed in geriatric or neurology memory consultation with a diagnosis of AD, VaD or a memory complaint without diagnosis of neurocognitive disorder. Inclusion criteria were an age over 70 years old, having a diagnosis of VaD, AD or memory complaint without diagnosis of neurodegenerative disorder confirmed by standardized cognitive tests, having a brain MRI performed within the previous year or planned. Patients with a severe dementia (MMSE < 11/30), another aetiology of dementia, delirium, a permanent atrial fibrillation, carotid stenosis or a history of carotid surgery, psychiatric disorders, any decompensated acute disease, under guardianship or curatorship, with a contraindication to MRI or refusing to participate were excluded.

Patients were identified during a follow-up visit by their usual geriatrician or neurologist. Then, investigator of the study checked the inclusion/exclusion criteria in the medical records and called the patient to give information about the study. In case of phone agreement, a visit was planned with the patient and their main caregiver to provide written and oral information, to check the inclusion and exclusion criteria and to include the patient in the study.

Demographic data (age, sex) and comorbidities such as history of smoking, hypertension, diabetes mellitus, dyslipidaemia, early cardiovascular family history, documented coronary artery disease, ischemic stroke and depressive disorder were collected. Glomerular filtration rate (GFR) was estimated by the CKD-Epi formula and chronic kidney disease was defined as a GFR lower than 30 ml/min/m<sup>2</sup>.

For each patient, the peripheral systolic blood pressure (SBP), the peripheral diastolic blood pressure (DBP) and the heart rate (HR) were measured at rest using a brachial oscillometer (Omron® 750IT) and an electrocardiograph (Phillips®). Peripheral mean blood pressure (MBP) was calculated as  $MBP = (SBP + 2DBP)/3$ . Peripheral pulse pressure (pPP) was defined by brachial SBP – DBP.

The cognitive performance was assessed by MMSe score which was considered pathological if the result was below the minimum threshold defined for age and socio-cultural category. The diagnosis of AD and VaD was based on DSM-V criteria.

The following geriatric parameters were evaluated:

- Walking speed. A 4 meters walking speed  $\leq 0.8$  m/s was considered as slow and as a marker of frailty;
- Hand-grip strength, assessed by Jamar dynamometer. A low strength was defined according to threshold depending on sex and was considered as probable sarcopenia. If associated with low walking speed, patients were considered as highly probable sarcopenia;
- Physical activity, assessed according to QAPPA questionnaire. It was considered low if it lasted less than 75 min, moderate if it lasted between 75 and 300 min and high if it lasted more than 300 min;
- Frailty assessed according to Fried criteria (weight loss, hand-grip strength, gait speed, exhaustion and physical activity) was used to define the frailty status (non-frail, pre-frail, or frail);
- Recurrent falls, defined as at least two self-reported falls within the last 12 months;
- Basic activities of daily living (BADL) and instrumental activities of daily living (IADL), 6-items and 8-items assessments respectively. A loss in one or more BADL defined disability;
- 30-items Geriatric depression scale (GDS).

## **2. Main outcomes**

The main outcome of our study was to compare the absolute and relative viscosity of the CCA between patients with dementia (AD or VaD) and patients with memory complaint without diagnosis of neurocognitive disorder.

The secondary outcome was to compare the arterial stiffness of the CCA between patients with dementia (AD or VaD) and patients with memory complaint without diagnosis of neurocognitive disorder.

## **3. Assessment of vascular function and structure**

The vascular explorations visit lasts 1h30 and allows, to assess non-invasively the following vascular parameters.

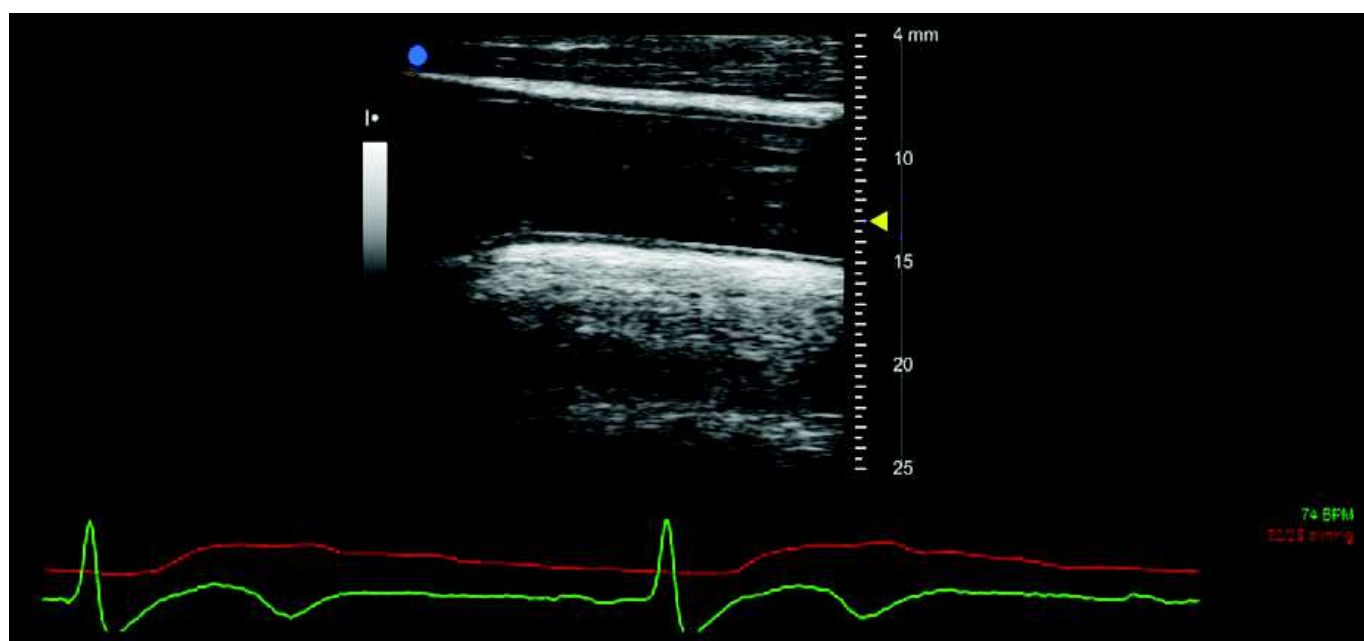
### **a. AWV**

The realization of the pressure and diameter hysteresis loops required the cooperation of 2 operators to carry out the measurement of local pressure by arterial tonometry on the CCA and the measurement of arterial diameter by high resolution echo-tracking at the same level of the contralateral CCA.

Applanation tonometry (Millar PCU2000® / PowerLab®) allows a non-invasive measurement of central arterial pressure variations using a piezo electric quartz pressure transducer. The principle of applanation states that the force required to flatten the wall of a cylinder, here an artery, is equal to the pressure inside the cylinder. This tonometer is connected to a classic preamplifier (Millar PCU2000®) transferring the electrical signal on the one hand to a computer via a data acquisition system (PowerLab®) for the visualization of pressure curves and on the other hand to the high-resolution ultrasound system (Vevo 3100®) via an interface (THM 150®) (Figure 2). An automatic calibration of the signal is carried out by the ultrasound system allowing to switch from an electrical signal in Volts to a pressure signal in mmHg.

The ultrasound probe used on the Vevo 3100® is a linear multi-array probe (MX250) and has an emission frequency of 21 MHz. This system generates a signal-based image on 256 greys levels with an axial resolution of 75 µm. The acquisition is made in two-dimensional mode at a repetition rate of 100 images per second for a maximum number of 1000 images per acquisition lasting 10 seconds. The Vevo 3100® also allows visualization of the patient's ECG signal using an interface (THM 150®).

A perfect synchronization of the 2 operators was necessary during the 10 seconds of recording to obtain an acquisition usable for the measurement of the AWW.



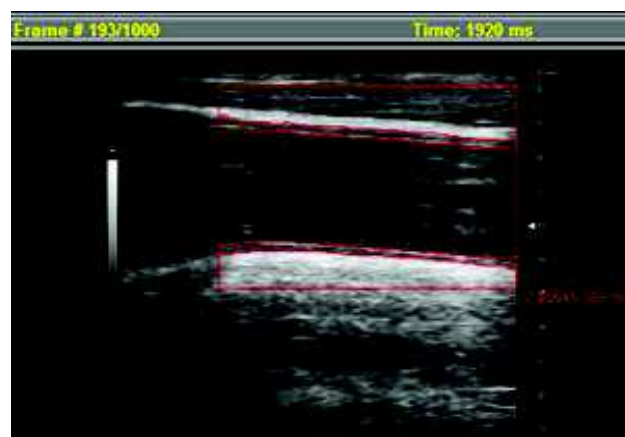
**Figure 2:** Simultaneous acquisition of ultrasound 1 cm upstream of the carotid bifurcation, contralateral carotid tonometry (red line) and ECG signal (green line) on the Vevo 3100®.

Then blood pressure and carotid ultrasound data are transferred to image processing software (VevoLab® and VevoVasc®), allowing to measure the inter adventitial arterial diameter and the Intima-Media Thickness (IMT). Each pixel of the image corresponds to a level of grey on a scale ranging from 0 = black to 256 = white which reflected the echogenicity of the tissue interfaces encountered by the ultrasound beam

which is delivered by the ultrasound probe. Thus, on one of the acquisition images, a manually delineated region of interest (ROI) encompassing the carotid arterial segment is defined. In this ROI, the arterial wall as well as the IMT is automatically detected by the VevoVasc® image analysis software based on their grey levels. The image analysis software then “follows” each pixel corresponding to the wall and to the IMT on the different images, making it possible to obtain the variations in inter adventitial diameter and IMT during the whole of acquisition (Figures 3 and 4).

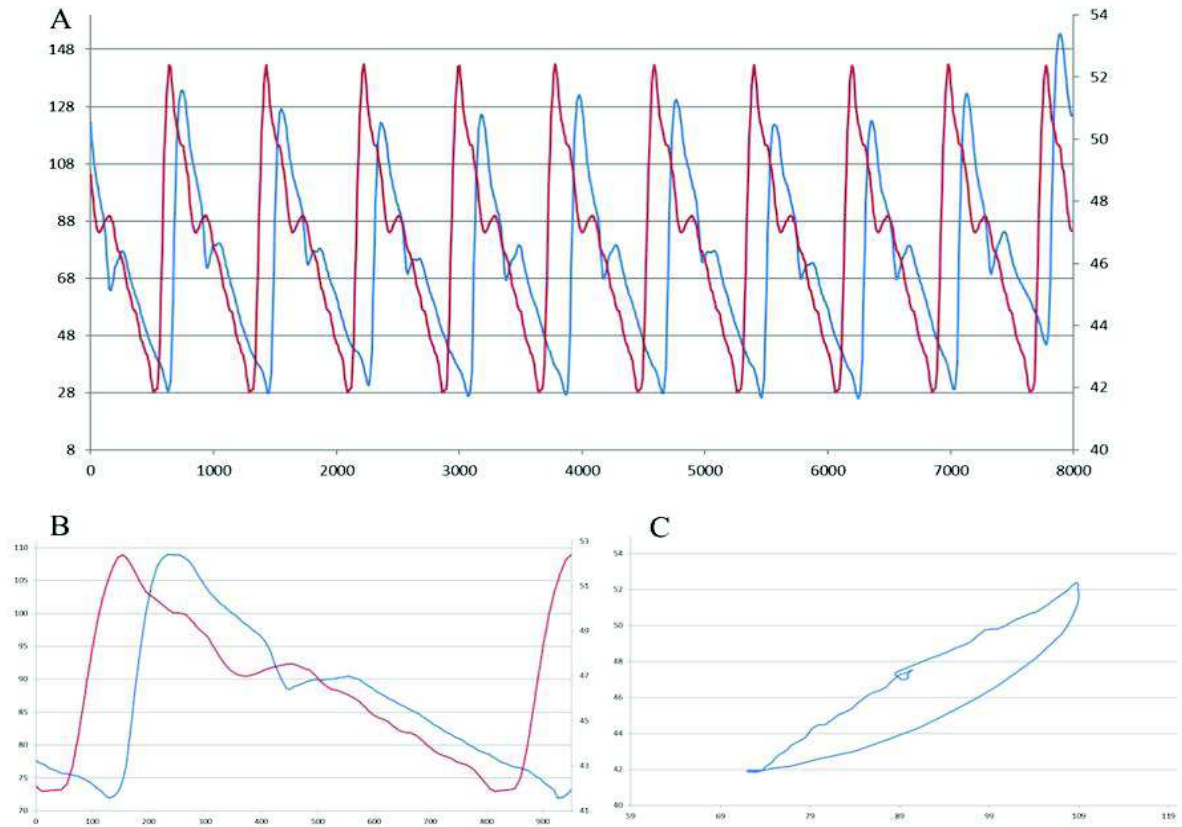


**Figure 3:** Manual definition of the desired area of interest represented by the red square (ROI). Automatic detection of the inter adventitial diameter, including the IMT, delimited by the two red lines.

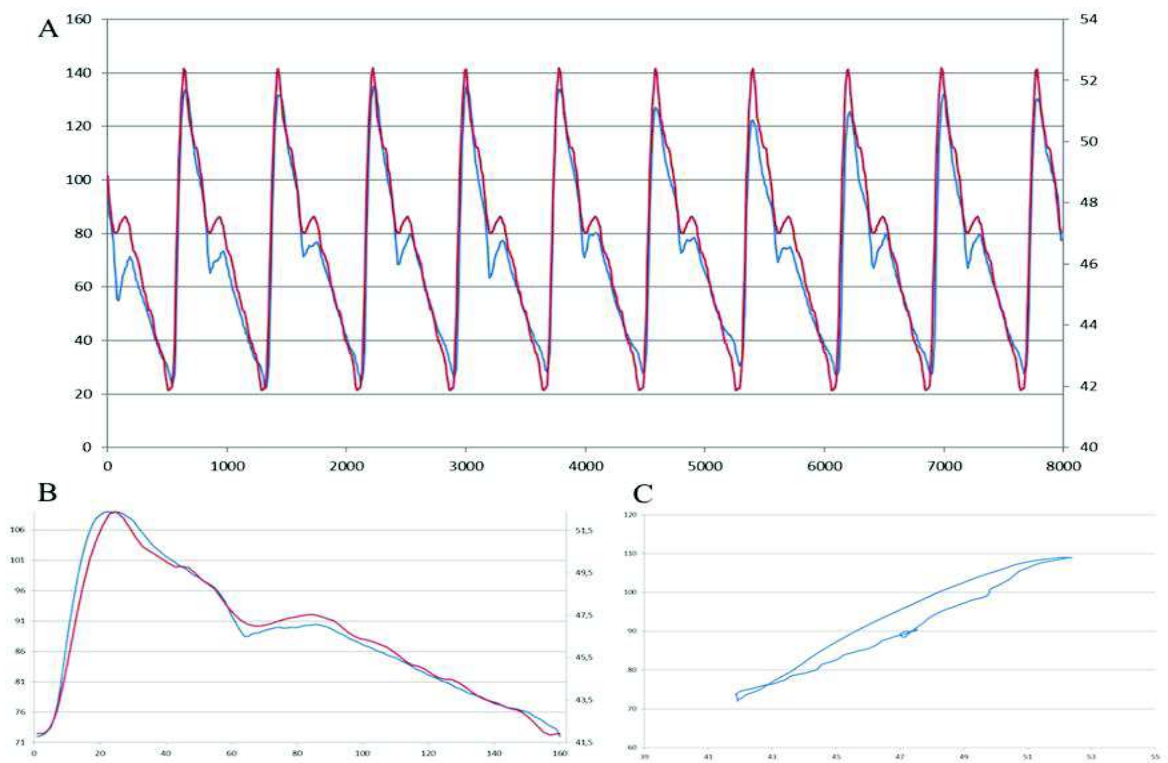


**Figure 4:** Manual definition of the desired area of interest represented by the red rectangle (ROI). Automatic detection of the intima-media thickness delimited by the double lines surrounding the IMT.

The automation of acquisition processing and calculations of arterial mechanics parameters has been developed using Excel® macro developed in our laboratory, allowing these steps to be carried out more quickly, from approximately 30 minutes to 3 minutes. Each cycle is delimited automatically, and the corresponding P-LCSA loop is generated by the foot-wave synchronization method with the possibility of manually adapting the synchronization of the waves if necessary (Figures 5 and 6).

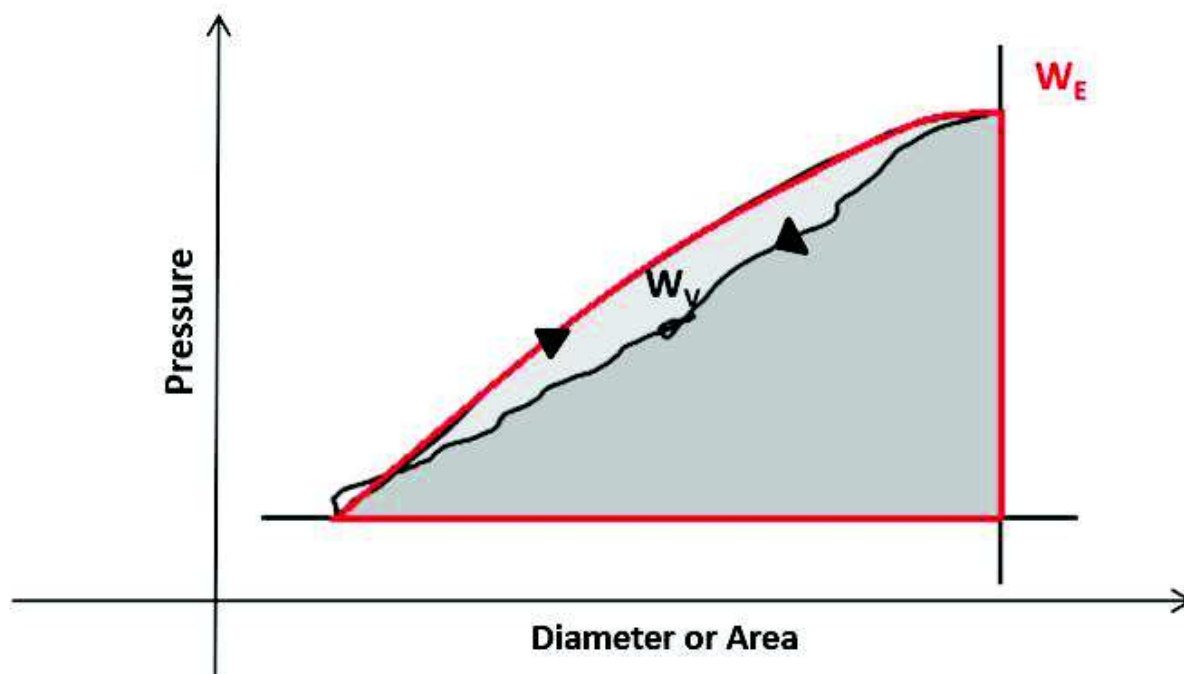


**Figure 5:** Asynchrony of pressure curves in mmHg (blue) and LCSA curves in mm<sup>2</sup> (red) as a function of time over the entire acquisition (in ms) (A), over a pressure and LCSA cycle (B) and the resulting P-LCSA loop (C).



**Figure 6:** Curves of pressure in mmHg (blue) and LCSA in mm<sup>2</sup> (red) as a function of time over the entire acquisition (in ms) (A), over a pressure and LCSA cycle (B) and the resulting P-LCSA loop after the synchronization of the wave feet (C).

Finally, the AWW is evaluated by planimetry (Image J®), the area of the hysteresis loop corresponding to the absolute viscosity ( $W_V$ ) and the area under the loading phase curve corresponding to the elastic energy stored ( $W_E$ ), allowing the calculation of the relative viscosity ( $W_V/W_E$ ) (Figure 7).



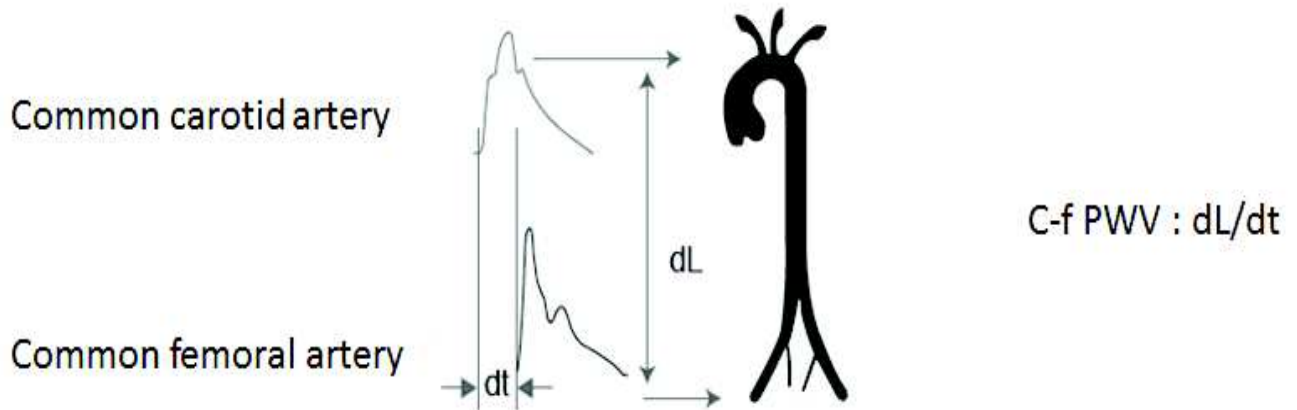
**Figure 7:** Schematic representation of the measurement of hysteresis loop and elastic energy stored.

The short-term intra-observer repeatability of the AWW measurement was assessed previously in 10 volunteers aged 27 to 57 years (median at 29 years). The coefficient of variation (CV) of  $W_V$  was  $13.5 \pm 8.0\%$  [5.0 – 29.9], the CV of  $W_E$  was  $9.9 \pm 4.9\%$  [2.1 – 15.6] and the CV of  $W_V/W_E$  was  $11.3 \pm 4.5\%$  [4.7 – 19.2]. The average estimated Lin's correlation coefficient (LCC) of  $W_V$  was 0.952 [0.846 – 0.986], the average estimated LCC of  $W_E$  was 0.974 [0.903 – 0.993] and the LCC of  $W_V/W_E$  was 0.854 [0.552 – 0.958]. Bland and Altman graphs showed good clinical agreement for the  $W_V/W_E$  and excellent clinical agreement for the  $W_E$  and for the  $W_V$  measurement.

## b. Arterial stiffness

### i. PWV

Arterial stiffness was evaluated by c-f PWV (Sphygmocor®). Pressure waveforms are obtained consecutively and non-invasively at the level of the right CCA and femoral artery and synchronized on the electrocardiograph signal. Thus, the ratio between the distance (dL) between the two sites of measurement and the time (dt or transit time) between the feet of the two waveforms (Figure 8) is calculated as c-f PWV = dL(meters)/dt(seconds).



**Figure 8:** Measurement of carotid-to-femoral PWV with the foot-to-foot method.

### ii. Impedance cardiography

Systemic hemodynamics and cardiac parameters were evaluated by impedance cardiography (PhysioFlow® PF-05 lab1TM, Manatec Biomedical®). The following parameters were obtained: stroke volume index, ejection fraction and cardiac index. Moreover, aortic stiffness and aortic distensibility were evaluated using Eorta® software.

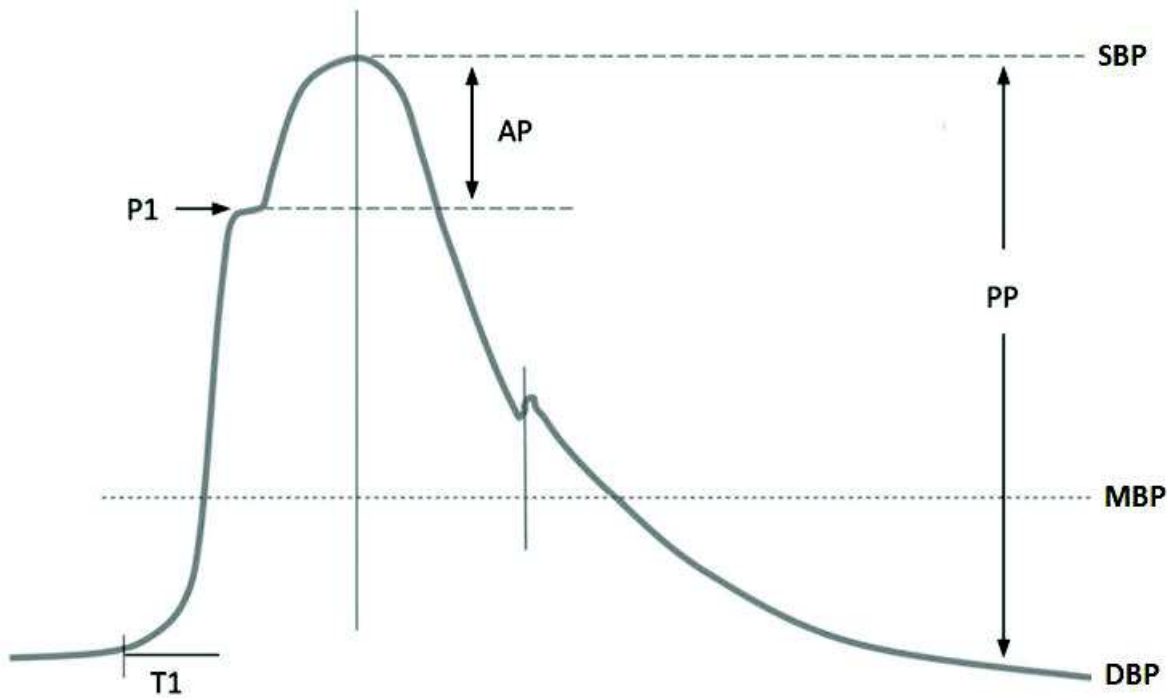
### c. Local carotid assessment of geometry, elastic properties and pulse wave analysis

Geometry of the carotid artery was assessed with echo-tracking (Vevo 3100®). Mean internal diameter ( $d_i$ ) and IMT were measured at the level of carotid posterior wall, 1 cm beneath the carotid bifurcation.

Elastic properties were obtained as follow: carotid distension was defined as the difference between systolic and diastolic internal diameter ( $d_{i\_max} - d_{i\_min}$ ) and was expressed as absolute value or as percent change ( $(d_{i\_max} - d_{i\_min}) \cdot 100 / d_{i\_min}$ ). The distensibility (DC) was estimated through the variations in arterial cross-sectional area and blood pressure, assuming the lumen to be circular as  $DC = \Delta LCSA / (LCSAd \cdot \Delta P)$ , where  $\Delta LCSA$  is the arterial cross-sectional area,  $LCSAd$  is the diastolic lumen area and  $\Delta P$  is the change in



carotid blood pressure. The incremental Young's elastic modulus ( $E_{inc}$ ), an index of the carotid wall material stiffness was calculated as  $E_{inc} = \frac{3(1 + \frac{LCSA_d}{WCSA})}{DC}$ , where WCSA is the wall cross-sectional area.



**Figure 9:** Pressure waveform analysis.

Carotid pressure waveform, obtained by applanation tonometry, was analysed using the SphygmoCor® software (figure 9). Central Pulse Pressure (cPP) was obtained. P1 height is the pressure at the first shoulder of the pressure wave and corresponds to the forward pressure wave. Aortic T1 time (in ms) is the duration between the start of the wave and P1. The pressures difference between P1 and the maximum pressure during the systolic phase is the augmentation pressure (AP) and corresponds to the reflected pressure wave. Augmentation index (AIx) is the ratio between AP to central pulse pressure:  $AIx = (\frac{AP}{cPP}) \cdot 100$ . The AIx normalized to the HR at 75 beats/min was also reported. These indexes correspond to the intensity of the reflection and increase with arterial stiffness.

#### **4. Ethic and research protocol**

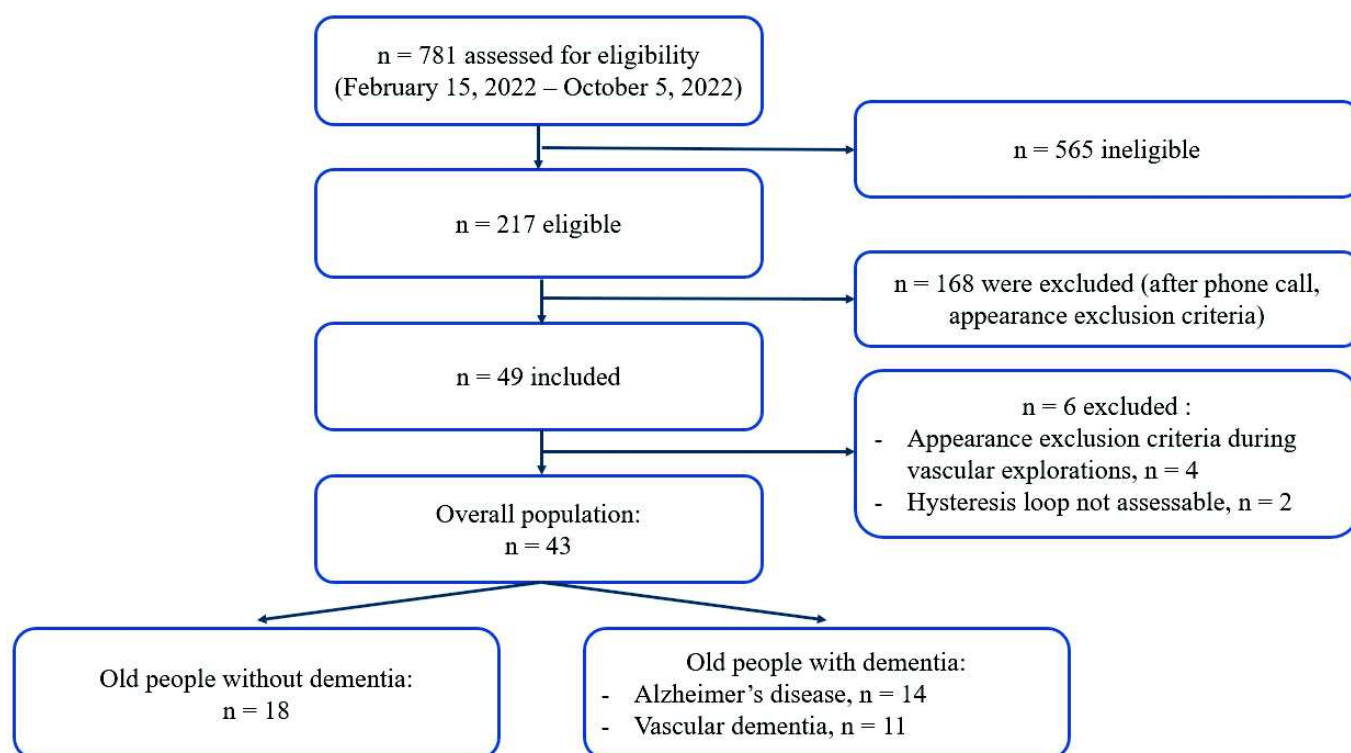
The protocol was approved by the CPP EST-II on April 12<sup>th</sup>, 2021. The clinical study is promoted by Rouen University Hospital. The first patient was included on February 15<sup>th</sup>, 2022. The inclusion period is planned over 2 years. The expected inclusion frequency is 6 volunteers per month.

## 5. Statistical analysis

The population was divided into 2 groups “dementia” and “no dementia”. Results are presented as median [IQR 25-75] or absolute value and percent (%). The 2 groups were compared with a Fisher’s test (or  $\text{Khi}^2$  as appropriate) for qualitative variables and by a Kruskal-Wallis rank sum test for quantitative variables. A p-value  $<0.05$  was considered significant. Statistics were performed using the R studio 1.4.1106 software.

## VIII. RESULTS

### 1. Baseline characteristics of the population



**Figure 10:** Flow-chart of the study.

Forty-three patients (27 women, 63%) were included with a median age of 80 [76.1 - 85.5] years old. Baseline characteristics of the population are shown in Table 1. Median BMI was 24.5 [22.2 - 27.6] kg/m<sup>2</sup>. Hypertension and dyslipidaemia were frequent in our population (respectively 60% and 58%). Other comorbidities were diabetes (14%), documented coronary artery disease (12%), moderate or severe chronic kidney (29%) and ischemic stroke (26%). Depression was common (13 patients, 30%). In our population, 18 patients (42%) had no dementia and 25 (58%) had dementia, including 14 (33%) with AD and 11 (25%) with VaD (Figure 10). There was no difference between patients with or without dementia regarding the baseline characteristics. The diagnosis of dementia was made 3 [2.05 - 4.91] years after the appearance of the first symptoms. Median MMSe of the overall population was 24 [20 - 27].

**Table 1:** Baseline characteristics of the population.

	Total population (n = 43)
Age, years	80 [76.1 - 85.5]
Women	27 (63%)
BMI, kg/m <sup>2</sup>	24.5 [22.2 - 27.6]
Living alone	17 (40%)
Smoking (past and current)	19 (44%)
Early cardiovascular familial history	7 (17%)
Diabetes mellitus	6 (14%)
Dyslipidaemia	25 (58%)
Hypertension	26 (60%)
One or more antihypertensive drugs	28 (65%)
Documented coronary artery disease	5 (12%)
Ischemic stroke	11 (26%)
Moderate or severe chronic kidney disease	12 (29%)
Depression	13 (30%)
Dementia	25 (59%)
• Alzheimer's disease	14 (33%)
• Vascular dementia	11 (26%)
MMSe score	24 [20 - 27]
Time between the first symptoms and the diagnosis of dementia, years	3 [2.05 - 4.91]

Results are expressed as Median [IQR 25 - 75] or n (%). BMI: Body Mass Index, MMSe: Mini mental state examination.

## **2. Comparison of the geriatric characteristics between patients with or without dementia (Table 2)**

MMSe was lower (20 [16 - 23] vs. 28 [26 - 28],  $p < 0.001$ ) in patients with dementia than in patients without dementia. BADL was similar between groups ( $p=0.1$ ) whereas IADL was lower in patients with dementia compared to those without dementia (2 [1 - 5] vs. 7 [5 - 8],  $p < 0.001$ ). Hand grip strength was similar between the two groups ( $p=0.5$ ). Walking speed was lower in patients with dementia (0.89 m/s [0.67 - 1.05] vs. 1.07 m/s [0.91 - 1.20],  $p=0.021$ ). Patients with dementia had more often no physical activity ( $p=0.01$ ) and were frailer ( $p=0.053$ ) than patients without dementia. Patients with dementia had more often undernutrition, depression, and falls in the past 12 months but these differences were not significant.

**Table 2:** Geriatric characteristics of patients according to the group (dementia or no dementia).

	No dementia (n = 18)	Dementia (n = 25)	P-value
MMSe score	28 [26 - 28]	20 [16 - 23]	<b>&lt; 0.001</b>
Education level			<b>0.012</b>
• Low	1 (5.6%)	8 (32%)	
• Mild	5 (28%)	11 (44%)	
• High	2 (11%)	3 (12%)	
• Very high	10 (56%)	3 (12%)	
BADL	6 [6 - 6]	6 [5 - 6]	0.10
IADL	7 [5 - 8]	2 [1 - 5]	<b>&lt;0.001</b>
Albuminemia (n = 16), g/L	40.6 [40 - 41.7]	38 [36.6 - 40]	<b>0.063</b>
Walking speed, m/s	1.07 [0.91 - 1.20]	0.89 [0.67 - 1.05]	<b>0.021</b>
Hand-grip strength, kg	24 [20 - 32]	26 [18 - 28]	0.5
Sarcopenia	6 (33%)	9 (36%)	>0.9
Falls in the last 12 months	1 (5.6%)	7 (28%)	0.11
Physical activity (QAPPA)			<b>0.01</b>
• No activity	2 (11%)	14 (56%)	
• Moderate	10 (56%)	6 (24%)	
• Intense	6 (33%)	5 (20%)	
Frailty (Fried criteria)			0.053
• Non-frail	12 (57%)	10 (40%)	
• Pre-frail	5 (28%)	6 (24%)	
• Frail	1 (5.6%)	9 (36%)	
Depression	3 (17%)	10 (40%)	0.2
Antidepressants	6 (33%)	14 (56%)	0.2
GDS	10 [8 - 12]	8 [5 - 14]	0.5

Results are expressed as Median [IQR 25 - 75] or n (%). Comparisons were performed with the Kruskal-Wallis rank sum test and the Fisher's exact test or  $\chi^2$  test as appropriate. BADL: Basic activity of daily living, IADL: Instrumental activity of daily living, QAPPA: Physical activity questionnaire for the elderly, MMSe: Mini mental state examination, GDS: Geriatric Depression Scale.

### **3. Comparison of the cardiovascular characteristics between patients with or without dementia (Table 3)**

Prevalence of hypertension, orthostatic hypotension and antihypertensive medications were similar between the two groups, except for diuretics, more frequent in patients with dementia.

Systemic hemodynamics such as SBP, DBP, MBP, HR were similar between the two groups. pPP tends to be higher in patient with dementia ( $p=0.056$ ) but not cPP.

The c-f PWV, the augmentation index (AIx), a marker of pressure wave reflection and AIx 75 were also similar between groups (10.70 m/s [9.90 - 12.20] vs 10.40 m/s [9.83 - 11.17],  $p=0.4$ ; 17% [13 - 25] vs 13% [8 - 24],  $p=0.3$  and 21% [14 - 25] vs 17% [12 - 27],  $p=0.7$ ).

Geometry of the common carotid artery, including IMT and diameter were similar between groups. Common carotid artery elastic properties assessed by distensibility (16.7 [11.4 - 18.5] vs 18.5 [13.4 - 23.2],  $p=0.15$ ) and elastic modulus (Einc) (162 [128 - 196] vs 150 [129 - 178],  $p=0.7$ ), a marker of the intrinsic stiffness of the arterial wall, were similar between groups.

The cardiac parameters such as ejection fraction, stroke volume index and cardiac index were similar between groups (61% [56 - 67] vs 56% [51 - 59],  $p=0.2$ ; 57 ml/m<sup>2</sup> [51 - 59] vs 48 ml/m<sup>2</sup> [45 - 57],  $p=0.087$  and 3.47 [3.11 - 3.78] vs 3.14 [2.82 - 3.54],  $p=0.12$ ). Aortic distensibility and aortic stiffness (3.57 [2.72 - 5.16] vs 3.58 [3.10 - 4.62],  $p=0.8$  and 20 [14 - 27] vs 18 [14 - 20],  $p=0.6$ ), assessed by bioimpedancemetry, were similar between the two groups.

**Table 3:** Cardiovascular characteristics of patients according to the group (dementia or no dementia).

	No dementia (n = 18)	Dementia (n = 25)	P-value
Hypertension	8 (44%)	18 (72%)	0.11
One or more antihypertensive drugs	8 (44%)	20 (80%)	0.12
Beta-blockers	5 (28%)	10 (40%)	0.5
CCB	2 (11%)	6 (24%)	0.4
ACEi/ARB	6 (33%)	12 (48%)	0.4
Loop diuretics and thiazide diuretics	0 (0%)	7 (28%)	<b>0.030</b>
Orthostatic hypotension	3 (17%)	6 (24%)	0.7
SBP, mmHg	136 [127 - 154]	145 [136 - 151]	0.3
DBP, mmHg	71 [70 - 78]	71 [66 - 76]	0.7
MBP, mmHg	94 [88 - 100]	96 [92 - 100]	0.6
HR, beats/min	64 [60 - 74]	63 [59 - 73]	0.6
pPP, mmHg	65 [58 - 73]	71 [65 - 78]	0.056
cPP, mmHg	60 [56 - 72]	67 [57 - 78]	0.3
pPP/cPP	1.01 [0.95 - 1.07]	1.00 [0.97 - 1.04]	0.4
Augmentation index, %	13 [8 - 24]	17 [13 - 25]	0.3
AIx75, %	17 [12 - 27]	21 [14 - 25]	0.7
IMT, $\mu\text{m}$	753 [658 - 846]	799 [666 - 860]	0.6
Mean internal diameter, mm	6.14 [5.57 - 6.65]	6.07 [5.52 - 6.62]	0.8
Distension, mm	0.54 [0.39 - 0.68]	0.43 [0.33 - 0.64]	0.4
Percent distension, %	10.2 [6.1 - 11.5]	8.6 [5.5 - 11.2]	0.5
Distensibility, MPa	18.5 [13.4 - 23.2]	16.7 [11.4 - 18.5]	0.15
Elastic modulus, kPa	150 [129 - 178]	162 [128 - 196]	0.7
PWV, m/s	10.40 [9.83 - 11.17]	10.70 [9.90 - 12.20]	0.4
Ejection fraction, % (n = 40)	56 [51 - 59]	61 [56 - 67]	0.2
Stroke volume index, ml/m <sup>2</sup> (n = 40)	48 [45 - 57]	57 [51 - 59]	0.087
Index cardiac, l/min/m <sup>2</sup> (n = 40)	3.14 [2.82 - 3.54]	3.47 [3.11 - 3.78]	0.12
Aortic distensibility (n = 40)	3.58 [3.10 - 4.62]	3.57 [2.72 - 5.16]	0.8
Aortic stiffness (n = 40)	18 [14 - 20]	20 [14 - 27]	0.6

Results are expressed as Median [IQR 25 - 75] or n (%). Comparisons were performed with the Kruskal-Wallis rank sum test and the Fisher's exact test or  $\text{Khi}^2$  test as appropriate. CCB: Calcium channel blocker, ACEi/ARB: Angiotensin-Converting Enzyme inhibitors/Angiotensin II Receptor Blockers. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure, HR: Heart rate, pPP: Peripheral pulse pressure, cPP: Central pulse pressure, AIx75: Augmentation index normalized to heart rate at 75 beats/min, IMT: Intima-media thickness, PWV: Pulse wave velocity.



#### 4. Comparison of the AWW between patients with or without dementia (Table 4)

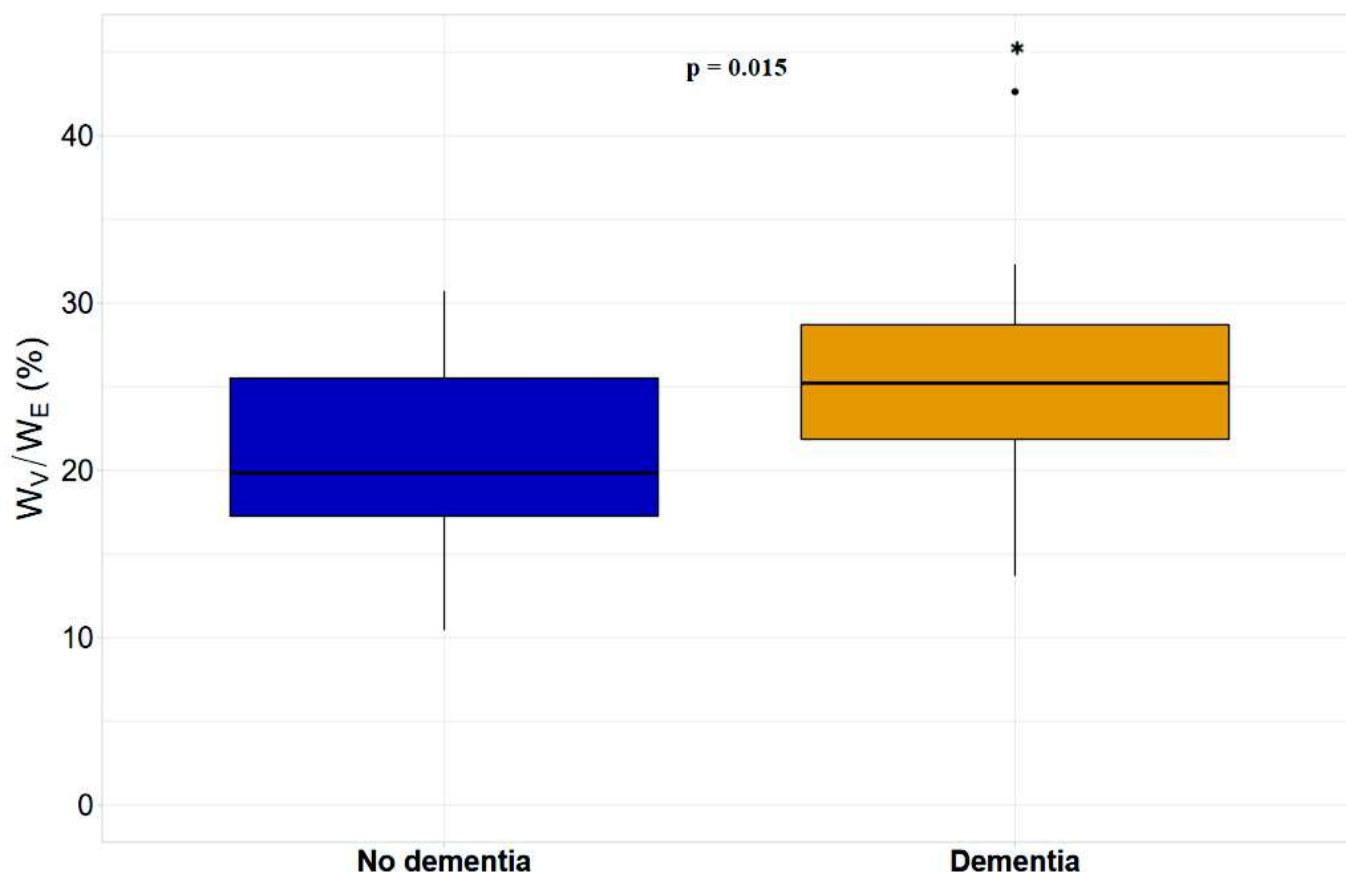
The absolute viscosity ( $W_V$ ) and the elastic energy stored ( $W_E$ ) were similar between the two groups ( $W_V$ : 38 mmHg.mm<sup>2</sup> [25 - 56] vs. 31 mmHg.mm<sup>2</sup> [19 - 45],  $p=0.3$  and  $W_E$ : 137 mmHg.mm<sup>2</sup> [108 - 203] vs. 156 mmHg.mm<sup>2</sup> [106 - 215],  $p=0.9$ ).

However, the relative viscosity ( $W_V/W_E$ ) was higher in patients with dementia than in patients without dementia ( $W_V/W_E$ : 25.2% [21.9- 28.7] vs. 19.9% [17.3 – 25.5],  $p=0.015$ ) (figure 11).

**Table 4:** AWW of patients according to the group (dementia or no dementia).

	No dementia (n = 18)	Dementia (n = 25)	P-value
$W_V$ , mmHg.mm <sup>2</sup>	31 [19 - 45]	38 [25 - 56]	0.3
$W_E$ , mmHg.mm <sup>2</sup>	156 [106 - 215]	137 [108 - 203]	0.9
$W_V/W_E$ , %	19.9 [17.3 - 25.5]	25.2 [21.9 - 28.7]	<b>0.015</b>

Results are expressed as Median [IQR 25- 75]. Comparisons were performed with the Kruskal-Wallis rank sum test.  $W_V$ : dissipated viscous energy or absolute viscosity,  $W_E$ : stored elastic energy,  $W_V/W_E$ : relative viscosity.



**Figure 11:** Comparison of  $W_V/W_E$  between patients with or without dementia. Comparisons were performed with the Kruskal-Wallis rank sum test ( $p=0.015$ ).  $W_V/W_E$ : relative viscosity.

## **IX.DISCUSSION**

This preliminary work is the first to investigate the impact of common carotid AWW on a peripheral target: the brain. Our results show a higher relative viscosity ( $W_V/W_E$ ) in patients with dementia without significant differences in arterial stiffness.

We choose to assess AWW and arterial stiffness of CCA because this large conductance elastic artery is known to have reduced elastic properties with aging. CCA are also the main arteries implied in the brain perfusion and are thus at the forefront of damping the pressure wave coming from the heart. Viscous behaviour was evaluated by the hysteresis loop of the pressure diameter relationship obtained using validated high resolution echo tracking method and tonometry. This method, based on a thermodynamic approach, has been already used in previous study in our laboratory (Roca and al. 2018, 2022), but also in another team (Giudici and al. 2021) and in animal model (Boutouyrie and al. 1997). Because our previous studies were performed with a different echo-tracking device, we validated our methodology and the repeatability of AWW measurement before the start of the study (L. Zmuda, Master 2).

With this thermodynamic approach, we were able to evaluate the energy exchanged within the arterial wall. We expressed the viscous behaviour as the absolute value of energy dissipation but also relative to the elastic energy stored, one of its major determinants. Furthermore, we assessed the elastic behaviour of arteries with c-f PWV, a non-invasive method that is the gold standard of the assessment of arterial stiffness of large arteries (Laurent and al. 2006). In addition, we used other validated methodologies, such as pulse wave analysis, impedance cardiography or local CCA mechanical parameters, to assess elastic behaviour of CCA and to confirm our results.

In our study, diagnosis of dementia was based on DSM-V and was performed by trained neurologists and geriatricians, allowing a low level of misclassification in both groups.

In this preliminary study, we found a higher relative viscosity ( $W_V/W_E$ ) in patients with dementia compared to those without dementia. To our knowledge, no previous study explored the association between AWW and dementia or other target organs, limiting the comparison with literature. Some authors suggest that an increase in AWW could be responsible for an increase in energy dissipation within the arterial wall and thus in cardiocirculatory uncoupling (Boutouyrie and al., 1997). This increase in AWW could also result in a protective effect against peripheral organ damages by reducing the energy transmitted to the periphery. However, this hypothesis is not in accordance with our results. Another hypothesis is that the impairment of cardiovascular coupling could be responsible for an impairment in brain perfusion, thus resulting in cognitive decline (Avolio and al. 2018). In addition, the increase in AWW could be the consequences of the endothelial dysfunction (Roca et al. 2018, 2019), which has also been described as a mechanism favouring dementia (Toth and al. 2017; Avolio and al. 2018). All these hypotheses need to be assessed in future studies. In our study, the increase in relative viscosity in patients with dementia could also be partly explain

by a lower physical activity in this group. Indeed, physical activity could prevent an increase in AWV in old people (Kawano and al. 2013). For this reason, the final analysis of our study will be adjusted on the QAPPA.

Some other factors could be confounding factors with our assessment of AWV. Fortunately, we did not observe differences in baseline comorbidities or systemic hemodynamics between the two groups. Thus, this limits the risk of bias in the interpretation of our results about AWV. In fact, hypertension, diabetes, or blood pressure values are known parameters influencing the values of  $W_v$  (Armentano and al. 2006; Roca and al. 2019; Giudici and al. 2021). Moreover, arterial stiffness was similar between the two groups. This result was observed with different parameters assessing the elastic behaviour, such as c-f PWV, augmentation index, elastic modulus, distensibility or cardiac impedancemetry. This is not in accordance with previous works suggesting the link between arterial stiffness and neurocognitive disorders (Hanon and al. 2005; Kearney-Schwartz and al. 2009), but this difference could be explain by the small sample size of our study. In fact, we have only a third of our sample size calculated on the basis of c-f PWV obtained in previous studies (Hanon and al. 2005).

In any case, the association between dementia and increased AWV without increased arterial stiffness suggests that these two parameters should be assessed independently and give different information. This argues for the assessment of both arterial stiffness and AWV when assessing arterial mechanics.

Our study has some limits. First, this is a preliminary analysis of the VISCOG study. Thus, the findings need to be interpreted cautiously due to the small number of patients included. Based on our sample size calculation, we plan to include 140 patients, 55 patients with AD, 55 patients with VaD and 30 patients with memory complaint but without dementia, over the next 2 years. During the first eight months (33% of the inclusion period) of the study, we included 43 patients (31% of the sample size), which is in accordance with our expected rhythm of inclusion.

Moreover, our population was too small to perform adjustment in our statistical analysis, mainly on arterial stiffness or midwall stress. In the final analysis of the VISCOG study, this adjustment will permit to interpret the proper effect of the viscous properties independently of the change in elastic properties. Finally, our study is a cross sectional study that does not confirm the causality of the relationship and the impact of the AWV on the longitudinal cognitive decline.

Perspective of this work is to compare the AWV and arterial stiffness of CCA in the 3 groups: patients with memory complaint but without dementia, patients with AD and patients with VaD. In addition, in the VISCOG study, cognitive assessment is not limited to MMSe. Indeed, an assessment of specific cognitive domains such as memory, by the Grober test, executive functions, by the Rapid Frontal Efficiency Battery, language, by the Oral naming score or praxis, by the Brief Praxis Evaluation Battery is also performed. These results are not presented here, because some of these cognitive assessments are planned in the

following months. However, they will be presented in the final study. Finally, the comparison of AWW according to the findings on brain MRI will be performed.

In conclusion, these results suggest for the first time a link between the AWW and dementia. If these results are confirmed in the final study, other studies will be necessary to demonstrate the causality of this relationship in the cognitive decline. Moreover, it will be necessary to explore whether AWW modulation could be a promising target to limit the risk of dementia.

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## **RESUME :**

**Introduction :** Le vieillissement est caractérisé par une augmentation de la rigidité des artères de conductance. Cette altération des propriétés élastiques artérielles est associée au diagnostic de démence vasculaire (DVa) ou d'Alzheimer (DA). Cependant, les artères ont un comportement viscoélastique. La composante visqueuse, peu étudiée, se manifeste par un décalage entre les courbes systolique et diastolique de la relation pression-surface artérielle, qui réalise une boucle d'hystérèse dont la surface représente l'énergie visqueuse dissipée à chaque cycle cardiaque ( $W_V$ ). Aucune étude n'a évalué l'association entre la viscosité pariétale artérielle (VPA) et la DVa ou la DA.

**Objectif :** L'objectif principal de l'étude était de comparer la VPA et la rigidité artérielle de l'artère carotide commune des patients présentant une démence (DVa ou DA) à ceux ne présentant pas de démence. L'objectif final de l'étude sera de comparer la VPA entre les 3 groupes : DVa, DA et absence de démence.

**Méthodes :** Dans cette étude prospective, transversale, monocentrique, 43 patients de plus de 70 ans présentant une démence (n=25) ou indemne de démence (n=18) ont été inclus. Les boucles pression-surface ont été obtenues par tonométrie couplée à une échographie carotidienne haute résolution controlatérale. La VPA a été évaluée par planimétrie et exprimée en valeur absolue de  $W_V$  ou relativement à l'énergie emmagasinée par la paroi artérielle au cours du cycle ( $W_V/W_E$ ). La rigidité artérielle a été évaluée de façon non invasive par la vitesse d'onde de pouls carotido-fémorale (VOP c-f)

**Résultats :** L'âge médian des patients était de 80 ans [76.1 - 85.5] (n = 27 femmes). Le MMSe médian était de 20 [16 - 23] dans le groupe des patients ayant une démence, et de 28 [26 - 28] pour ceux ne présentant pas de démence. Il n'y avait pas de différence entre les groupes concernant les principales comorbidités cardiovasculaires ou les chiffres de pression artérielle à l'état basal.  $W_V$  et  $W_E$  tendaient à être similaires dans les deux groupes ( $W_V$  : 38 mmHg.mm<sup>2</sup> [25 - 56] vs. 31 mmHg.mm<sup>2</sup> [19 - 45], p=0.3 et  $W_E$  : 137 mmHg.mm<sup>2</sup> [108 - 203] vs. 156 mmHg.mm<sup>2</sup> [106 - 215], p=0.9). Cependant, la viscosité relative ( $W_V/W_E$ ) était plus élevée chez les patients présentant une démence par rapport à ceux ne présentant pas de démence ( $W_V/W_E$  : 25.2% [21.9- 28.7] vs. 19.9% [17.3 - 25.5], p=0.015). La rigidité artérielle était similaire dans les deux groupes.

**Conclusion :** Les résultats préliminaires de cette étude suggèrent pour la première fois une association entre la VPA carotidienne et la démence.

**Mots-clés :** Vieillissement, viscosité pariétale artérielle, rigidité artérielle, démence.