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P wave duration in cryptogenic stroke: a case control prospective study: VPAC study

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**P WAVE DURATION IN CRYPTOGENIC STROKE : A CASE CONTROL
PROSPECTIVE STUDY
VPAC STUDY**

THÈSE POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

SPÉCIALITÉ : CARDIOLOGIE ET MALADIES VASCULAIRES

Par Mme Elodie DESCHAMPS

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 13/09/2021

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ABBREVIATIONS

ACEi = Angiotensin converting enzyme inhibitor

AF = Atrial Fibrillation

ARB = Angiotensin receptor blocker

ASCOD = A for atherosclerosis; S for small-vessel disease, C for cardiac pathology, O for other causes and D for dissection

BMI = Body mass index

CS = Cryptogenic stroke

CT = Computed tomography

ECG = Electrocardiogram

ESUS = Embolic stroke of undetermined source

FAM = Fibrotic atrial myopathy

HFpEF = Heart failure with preserved ejection fraction

IAB = Interatrial block

ILR = Implantable loop recorder

IS = Ischemic stroke

LA = Left atrium

LAS = Left atrial surface

LAVi = Left atrial volume indexed

LV = Left ventricle

LVEDD = Left ventricle end diastolic diameter

LVESD = Left ventricle end systolic diameter

MRI = Magnetic resonance imaging

OSA = Obstructive sleep apnea

PGLS = Peak of global longitudinal strain

PWD = P wave duration

TAPSE = Tricuspid annular plane systolic excursion

TEE = Transesophageal Echocardiography

TIA = Transient ischemic attack

TOAST = Trial of Org 10172 in Acute Stroke Treatment

TTE = Transthoracic Echocardiography

RESUME

Introduction - Les accidents vasculaires cérébraux (AVC) cryptogéniques représentent un défi en termes de prévention secondaire. Il est important d'identifier des marqueurs emboliques dans cette population afin de cibler les patients à risque d'évènement cardio-embolique et prévenir les récives. Cette étude évalue la durée de l'onde P, un marqueur non invasif de la fonction atriale, chez une population de patients ayant présenté un AVC étiqueté cryptogénique comparé à un groupe témoin indemne d'AVC.

Méthodes - Les patients âgés de 18 à 80 ans ayant bénéficié de la pose d'un holter implantable sous cutané entre janvier 2019 et Avril 2021 dans le cadre du bilan étiologique d'AVC cryptogénique ont été inclus. Parallèlement, un groupe témoin indemne d'AVC a été constitué en incluant des patients admis en hôpital de jour ou en consultation pour bilan cardiologique.

Le critère de jugement principal était la durée de l'onde P mesurée sur un ECG numérique 12 dérivations avec haute amplification. L'amplitude de l'onde P ainsi que différents paramètres échographiques de la fonction atriale ont été recueillis chez tous les participants.

Les patients du groupe AVC ont été suivis dans le temps afin de dépister la survenue de FA ou une récive d'AVC.

Résultats - 95 patients ont été inclus dans le groupe AVC et 96 dans le groupe contrôle. La durée de l'onde P était significativement allongée chez les patients du groupe AVC comparé au groupe témoin. Cette différence persistait après ajustement sur les facteurs confondants. Il existait une relation linéaire entre la durée de l'onde P et la surface de l'oreillette gauche chez tous les patients.

Pendant le suivi, 12% des patients du groupe AVC ont développé de la FA et 7 patients ont présenté une récive d'AVC. Il n'existait pas de différence significative sur les variables entre

ceux qui ont présenté de la FA ou une récurrence d'AVC et les autres. Les patients présentant des lésions ischémiques dans des territoires multiples ou d'âges différents avaient une durée de l'onde P significativement allongée par rapport aux autres.

Conclusion - La durée de l'onde P est augmentée chez les patients ayant présenté un AVC cryptogénique. La durée de l'onde P mesurée sur un ECG avec haute amplification pourrait être un nouvel indicateur non-invasif de risque cardio embolique et guider la stratégie anti-thrombotique dans cette population.

ABSTRACT

Introduction - Cryptogenic stroke (CS) represents a challenge for secondary prevention. Identification of embolic markers in this population is crucial to identify patients at risk of cardioembolic stroke and recurrence. This study evaluates the P wave duration (PWD) a non-fibrillatory atrial electrical marker in a population of patients with CS compared with a stroke-free control group.

Methods - Patients between 18 and 80 years old who had implantable loop recorder inserted between January 2019 and April 2021 for CS workup were included. At the same time, a stroke-free control group was constituted with patients admitted to the department of cardiology for cardiac evaluation. The primary end point was PWD measured on a 12-lead ECG with high amplification. P-wave amplitude and various echocardiographic parameters of atrial function were collected in all participants. Patients in the cryptogenic stroke group were monitored over time to detect AF occurrence or stroke recurrence.

Results - 95 patients were included in the stroke group and 96 in the control group. PWD was significantly increased in patients in the stroke group compared with controls. There was a linear relationship between PWD and LA surface in all patients. During follow-up, 12% of patients in the stroke group developed AF and 7 patients had recurrent stroke. There was no significant difference on any variable between those who developed AF or recurrent stroke and the others. Patients with recent and older ischemic lesions or in multiple territories had significantly prolonged P-wave duration compared with others.

Conclusion: - PWD is increased in patients with cryptogenic stroke. PWD measured on a high-amplification ECG could be a new noninvasive indicator of cardioembolic risk and guide the antithrombotic strategy in this population.

PART I :

CRYPTOGENIC STROKE : A REVIEW

Introduction

Definition and classifications

Stroke is defined as a sudden focal neurological deficit related to a cerebral perfusion defect. It can sometimes be transient with spontaneous recovery within a few hours and normal cerebral imaging, so-called transient ischemic attack (TIA). A distinction is made between ischemic stroke, which accounts for 85% of all strokes, and spontaneous hemorrhage for approximately 15%.

In order to guide therapeutic management at discharge, the TOAST classification (1) has been most widely used in the literature and differentiates:

- Large-artery atherosclerosis: stenosis > 50% or occlusion of a major brain artery due to atherosclerosis;
- Cardioembolism : related to a cardiac source
- Small-vessel occlusion : deep lacunar infarction and prior history of diabetes or hypertension;
- Stroke of other determined etiology: rare causes of stroke (vasculopathies, hypercoagulable states, or hematologic disorders);
- Stroke of undetermined etiology.

Cryptogenic stroke (CS) therefore refers to a stroke with unknown cause. The problem with this classification is that the latter includes patients who had an exhaustive workup, incomplete workup, or more than two equal possible causes.

With the advances in diagnostic management, new classifications have been proposed, such as the Causative Classification of Stroke system (CCS) (2) or the ASCOD classification (A for

atherosclerosis; S for small-vessel disease, C for cardiac pathology, O for other causes and D for dissection), which allows consideration of underlying etiologies for a given patient (3,4).

Epidemiologic data

The main causes of stroke are dominated by cardioembolic and cryptogenic subgroups (5). Stroke subtype repartition according to centers described by Bejot and al (*Béjot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Rev Neurol (Paris). 2016 Jan;172(1):59–68*) is illustrated in *Figure 1*.

CS account for 25% of all ischemic strokes, and up to 40% in young patients (6,7).

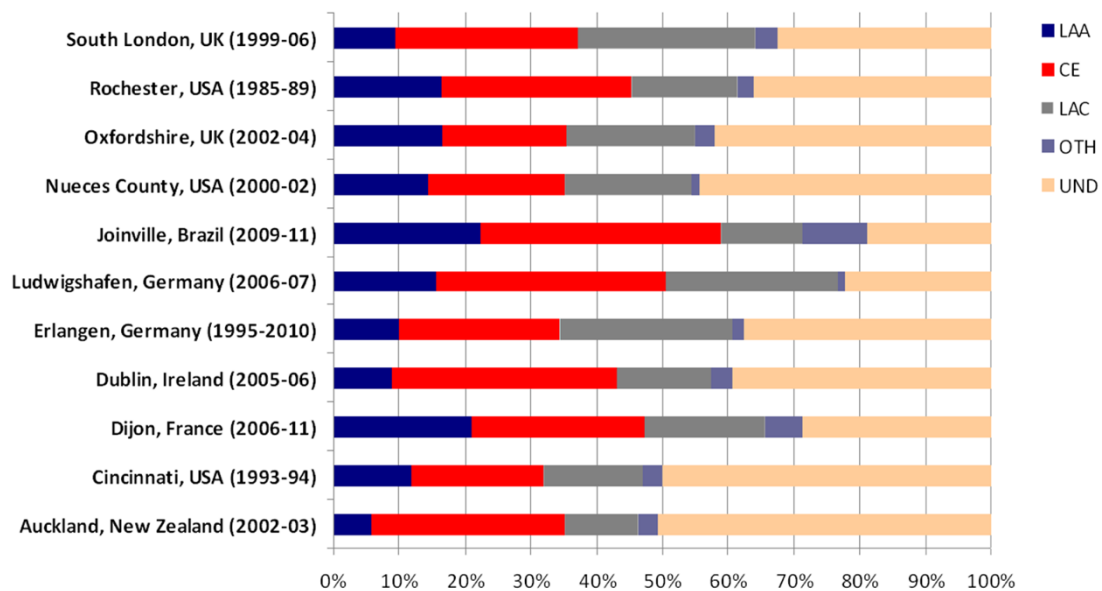


Figure 1 : Stroke subtype according to country from Béjot et al., Rev Neurol 2016. Abbreviations : LAA = large artery atherosclerosis ; CE = cardioembolic ; LAC = Lacunar ; OTH = other cause ; UND = undetermined cause

The risk of recurrence after ischemic stroke (IS) is highest in the first year (around 4,7%), and then stabilizes over time at 11% at 5 years and 16% at 10 years, as shown in *Figure 2* (8). There is limited data regarding recurrence rates after CS, but one study reported up to 30% at 1 year (9).

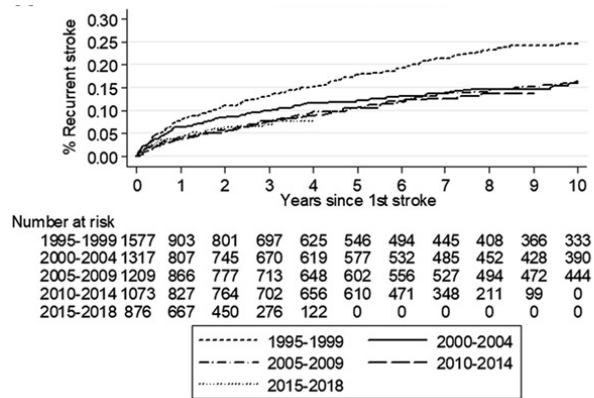


Figure 2 : Stroke recurrence over time, from Flach C and al., Stroke, 2020 (8).

Mortality rates after stroke are significant, up to 30% at 1 month with a poorer prognosis reported for cardioembolic causes (10).

Risk factors

Overall, IS shares the same risk factors as ischemic heart disease, i.e. hypertension, dyslipidemia, diabetes mellitus and smoking habit (11).

In contrast, CS is more frequent in younger patients without identified cardiovascular risk factors.

Diagnosis assessment of CS

Patients with CS have aspecific clinical presentations similar to other types of IS. Current guidelines suggest a minimal etiologic assessment to determine the most probable origin of the stroke (12).

The first step is brain imaging, which may be a computed tomography (CT) scan or brain magnetic resonance imaging (MRI). MRI is better for detection of small deep infarct,

particularly for diagnosis of small vessel disease but is not always accessible in the acute phase of stroke (13) (Figure 3).

There is no specific imaging evidence for CS, but presence of multiple superficial infarcts has been found in 60% of CS patients (14).

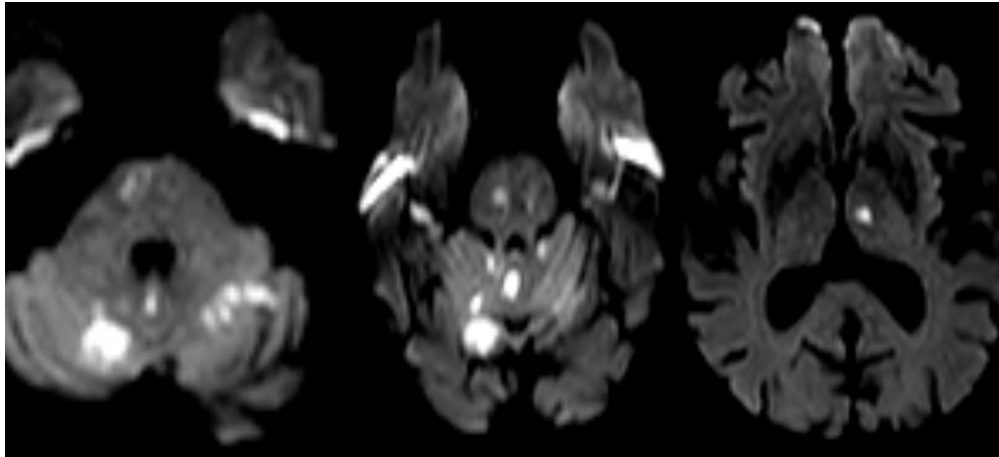


Figure 3 : Ischemic lesions in multiple territories in the same patient. From left to right: bilateral cerebellar lesions, right protuberance and left thalamic

Additional workup should include a non-invasive examination of the extra- and intracranial vessels, blood workup to rule out a coagulation disorder, and cardiac evaluation.

The cardiac examination comprises electrocardiogram (ECG), rhythm monitoring for at least 24 hours, and transthoracic echocardiography (TTE). Some centers also perform a transesophageal echocardiography (TEE) to identify certain cardio-embolic causes that are not apparent on TTE. CS is a diagnosis of exclusion that will be considered at the end of this complete workup.

Therapeutic management

Stroke management includes antiplatelet therapy in most cases. A specific management is proposed according to the identified cause. AF detection implies initiation of curative anticoagulation if the cardiovascular risk is significant. This risk is estimated by the CHADS VASC score (*Supplementary files*). Curative anticoagulation is recommended if the CHADS VASC score is >2 in women and >1 in men. Current treatment of CS consists of antiplatelet therapy and control of cardiovascular risk factors (15).

There is currently no evidence to support the use of curative anticoagulation in this population. Indeed, the concept of ESUS (Embolic Stroke of Undetermined Source) had been introduced in 2014 for a subgroup of patients among CS presumed to be of cardioembolic origin based on a combination of clinical and imaging evidence (16). Two large trials were conducted in this population to evaluate curative anticoagulation rather than antiplatelet therapy with negative results (17,18). Therefore, this subclassification does not appear to be optimal enough to select patients at high embolic risk.

Mechanism of CS: hypotheses

Because of their high prevalence, it is presumed that most of CS are related to cardioembolic causes.

Moreover, histological study of clot collected from patients with IS has shown similarities between thrombi found in cryptogenic and cardioembolic patients, and inversely significant differences in composition according to cardioembolic or noncardioembolic origins (19,20).

Based on these results, several studies have sought to identify an underlying cardioembolic cause.

AF and CS

Incidence of atrial fibrillation (AF) is increasing with population aging. Because of the absence of effective atrial contraction, left atrium is the site of hyperviscosity and blood stasis (two of the three factors of Virchow's triad), with a significant risk of embolization.

Stroke risk is therefore increased in the presence of AF and is estimated at 2 to 3 per 1000 person-years (21).

It has been hypothesized that a majority of CS is related to silent paroxysmal AF.

Thus, several techniques for prolonged monitoring have been developed, such as the implantable loop recorder (ILR) (*Figure 4*), which allows the recording of brief AF episodes with a life expectancy of 3 years (*Figure 5*). The CRYSTAL-AF study demonstrated AF detection rates of up to 30% with these devices (22).

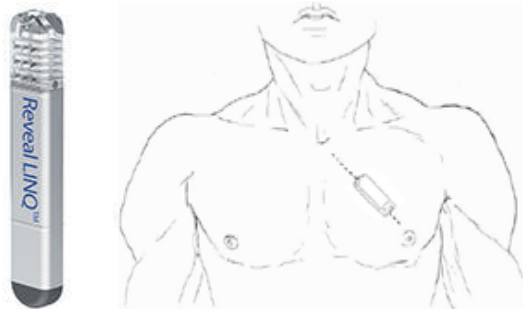


Figure 4 : MEDTRONIC device. Implantable loop recorder (ILR)

ILR is currently recommended for the tracking of silent AF in patients with a CS after an exhaustive workup as a class IIa B (23).

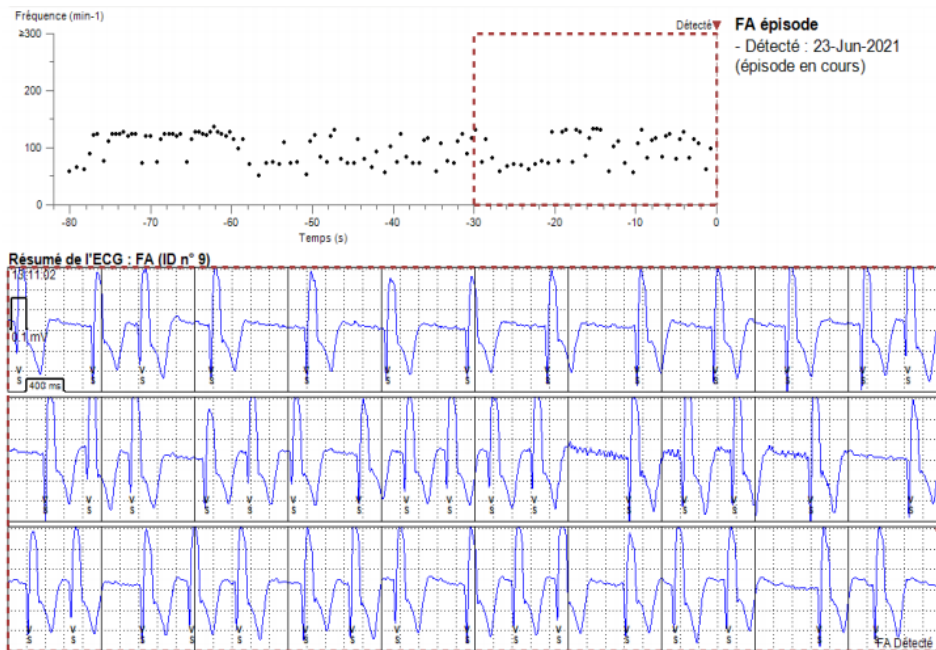


Figure 5 : Exemple of AF detection by ILR

Atrial cardiopathy and CS : time for a new paradigm

Recent studies have suggested that AF is not directly involved in stroke occurrence but may be a marker of atrial dysfunction (24).

Assessment of atrial function is not yet recommended in clinical practice but several markers have been evaluated recently (25–27).

A particular interest is given in this work to the P wave duration (PWD) and interatrial block (IAB). IAB is a conduction disorder between the left and right atriums across the Bachmann's bundle. This disturbance is characterized by a prolongation of the PWD > 120 ms on the surface ECG. A distinction is made between partial and advanced forms as illustrated in *Figure 6*.

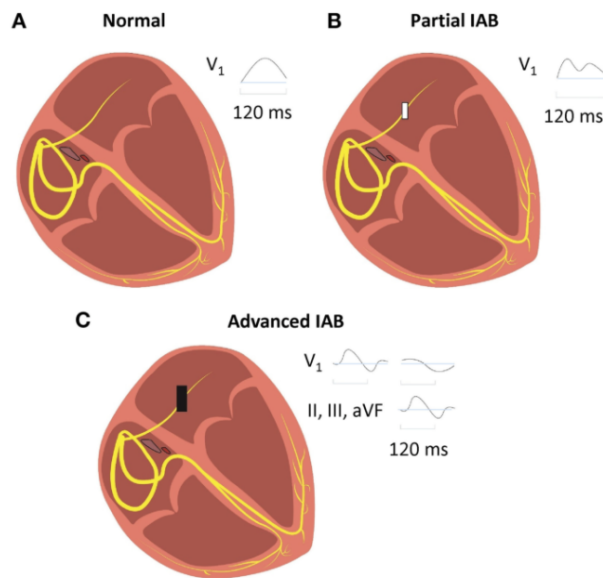


Figure 6 : Different stages of interatrial block (IAB), from Tse et al., 2016 (28)

PWD has been associated with the risk of cardioembolic stroke (28) but only a few data exists in CS or ESUS population with discrepancies (Table 1).

| Author, year | Tony Y W Li, 2021 | Moonki J, 2020 | Guiomar A, 2020 | Acampa M, 2018 | Vural M, 2015 | Cotter PE, 2011 |
|-------------------|-------------------|----------------|-----------------|--------------------|--------------------|--------------------|
| Country | Singapore | Korea | Barcelona | Italy | Turkey | United Kingdom |
| Enrollment period | 2014-2017 | 2015-2018 | 2015-2017 | | 2009-2010 | |
| Population | ESUS | ESUS | ESUS | Cryptogenic stroke | Cryptogenic stroke | Cryptogenic stroke |
| n | 181 | 250 | 75 | 222 | 80 (40/40) | 78 (55/23) |
| Control groupe | no | yes (pAF) | no | no | yes (healthy) | yes (healthy) |
| Primary outcome | Recurrent stroke | PWD | AF occurrence | AF occurrence | PWD | PWD |
| p value | 0,28 | 0,321 | 0,042 | < 0,05 | 0,02 | 0,013 |

Table 1 : Overvied of trials evaluating PWD in cryptogenic stroke/ESUS patients. pAF = paroxysmal AF ; AF = atrial fibrillation ; PWD = P wave duraton

Other causes

Patent foramen oval (PFO) with or without interatrial septal aneurysm is a major cause of stroke in young patients. This common anatomical variant is present in 25% of general population and is easily diagnosed by performing a TEE with contrast test (29).

Gap of evidence

Despite recent advances, a substantial number of patients with CS have no identified cause, and there remain unanswered questions.

AF is strongly associated with stroke risk, but its causality is now questioned and it seems to be part of a more general entity known as atrial cardiopathy.

Assessment of left atrial function is currently not performed in daily care, and whereas markers of atrial dysfunction have been shown to be associated with stroke risk, particularly embolic stroke, they are not specific of left atrium and have not been validated in large randomized trials. P-wave duration is a noninvasive marker that can be easily performed in routine. However, its utility for discriminating patients at high embolic risk among CS remains to be defined.

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Supplementary files

- **CHADS VASc score from ESC AF Guidelines 2016.**

| CHA ₂ DS ₂ -VASc risk factor | Points |
|--|--------|
| Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction | +1 |
| Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment | +1 |
| Age 75 years or older | +2 |
| Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin | +1 |
| Previous stroke, transient ischaemic attack, or thromboembolism | +2 |
| Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque | +1 |
| Age 65–74 years | +1 |
| Sex category (female) | +1 |

- **Different monitoring strategies and rate of AF detection**

| Type of monitoring | Setting | Invasive vs. noninvasive | Duration | Rate of detection of Atrial Fibrillation, % |
|--|------------|--------------------------|----------|---|
| Admission ECG | Inpatient | Noninvasive | N/A | 2.7 |
| Inpatient continuous telemetry | Inpatient | Noninvasive | 3–5 d | 5.5–7.6 |
| Holter monitor | Outpatient | Noninvasive | 24 h | 3.2–4.8 |
| | | | 48 h | 6.4 |
| | | | 7 d | 12.5 |
| Mobile continuous outpatient telemetry | Outpatient | Noninvasive | 21–30 d | 16–25 |
| Implantable loop recorders | Outpatient | Invasive | 6 mo | 9 |
| | | | 36 mo | 30 |

Extracted from Yaghi S, Elkind MSV. Cryptogenic stroke: A diagnostic challenge. *Neurol Clin Pract.* 2014 Oct 1;4(5):386–93.

PART II :

ARTICLE

BACKGROUND

Stroke is the second leading cause of death across the world just after heart disease, with an overall incidence of 258/100,000 per year (1).

In order to guide therapeutic management, the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification defined subtypes of ischemic stroke (IS) based on clinical features and further examinations. It differentiates large-artery atherosclerosis, cardioembolism, small vessel disease (lacunae), stroke of other determined etiology and stroke of undetermined etiology (2).

The cardioembolic subtype includes diverse causes, but almost one third of ischemic strokes are related to atrial fibrillation (AF) (3).

The prevalence of AF increases with the advancing age in the population (4). The attributable risk of stroke from AF is raised by a factor of 2 to 6 in studies, and stroke may be the first clinical manifestation of previous subclinical AF (5,6). AF-related strokes are associated more frequently with a worsened functional prognosis, or even death (7).

Considering the effectiveness of anticoagulation therapy in this indication, it is important to identify AF in stroke patients.

Routine assessment after stroke is usually completed with transthoracic echocardiography (TTE), between 24 and 72-hour of cardiac monitoring, biological workup and supra-aortic vessels imaging.

In selected patients, a transesophageal echocardiography (TEE) may also be performed to investigate alternative cardioembolic causes.

20 to 30 % of strokes remain unexplained after investigation and are termed cryptogenic.

The main issue is how to prevent stroke recurrence in cryptogenic stroke (CS) patients. In fact, it has been reported up to 30% of recurrence according to studies (8).

Several trials have focused on screening for silent AF in this population. The development of implantable loop recorder (ILR) has improved the rate of AF detection up to 30% after CS (9,10). ICM is recommended as part of the post stroke assessment in CS patient with high suspicion of cardioembolic cause (11).

Although these findings are promising, there remain uncertainties about the causality of these AF episodes in stroke occurrence.

First, there is a lack of temporality between AF detection and stroke. Some patients have developed AF more than 1 year after the ischemic event. Some studies in patients implanted with pacemaker devices have shown that only a few patients experienced arrhythmias in the month prior to the incident ischemic stroke (12,13).

In addition, AF is usually defined as an episode lasting more than 30 seconds. Therefore it is unclear whether brief AF episodes can be considered as the main cause of stroke.(12,14).

Finally, AF and stroke share the same risk factors and affect patients at high cardiovascular risk. Thus, AF is found in nearly 15% of patients with small vessel disease (15).

These findings suggest that AF alone may not be the direct cause of stroke but rather a marker of atrial dysfunction. Atrial cardiomyopathy is defined as any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations (16). Atrial cardiomyopathy is common in CS patients and appears to be a major risk factor for stroke, regardless of AF (17).

There is currently no validated method for quantification of atrial function in clinical routine.

Several electrocardiographic and echocardiographic markers have been shown to be associated with stroke occurrence even in the absence of AF(17–19).

One of these parameters is the presence of interatrial block (IAB), first documented by Bayes de Luna, defined as the prolongation of electrical conduction time between the left and right atrium. It results in a P wave duration (PWD) greater than 120 ms on electrocardiogram (ECG) (20). IAB is frequently encountered in general population and is associated with a higher risk of AF occurrence (21). Recently, IAB has shown an association with ischemic stroke risk. However, studies have included cardioembolic strokes and only limited data exists in CS population with inconsistent results (22).

The purpose of this prospective case control study was to analyze P wave duration in patients with CS versus a stroke-free control group, and to evaluate its relationship with other potential markers of atrial dysfunction.

METHODS

The study protocol was approved by our institutional ethics board and complied with patient's non-opposition form.

Study population

Patients between 18 and 80 years old who have previously received an ILR for cryptogenic stroke from January 2019 to April 2021 were enrolled in our department.

Stroke was considered based on clinical features and cerebrovascular imaging in acute phase, which could be computed tomography (CT) scan or magnetic resonance imaging (MRI). All decision of ILR have been made during multidisciplinary meeting with neurologists and cardiologists in accordance with current guidelines (11).

Each patient of the study group was matched 1:1 by age and sex to control participants who were free from stroke. Participants from the matched control group were selected among patients admitted in hospital for diverse reasons depicted in *Supplementary files*.

Exclusion criteria in both groups were a history of cardiac surgery or left atrial appendage closure.

Patients in control group with previous stroke history, preexisting atrial fibrillation or heart failure with reduced ejection fraction (HFrEF) were excluded.

Demographic and anthropometric data, medication, traditional cardiac risk factors and co-morbidities were collected.

Reviewing of cerebral imaging

The brain imaging of initial incident stroke was reviewed by three expert neurologists blinded to patients' clinical details.

In accordance with the recent ASCOD criteria (23), we classified strokes based on infarct territorial (cortical, subcortical, supra and infratentorial), ipsilateral atherosclerotic stenosis > 50%, lacunae evocator of small vessel disease, multiple territory or recent and older lesions.

Digital amplified ECG measurement

The primary outcome was the comparison of PWD between CS and controls.

All ECG were obtained using Schiller AT-104 PC (Schiller, Baar, Switzerland) calibrated at 10 mm/mV with a speed of 25 mm/s and no additional noise filtering.

They were then transferred to a Sema software (Schiller, Baar, Switzerland) for analysis. For better identification of the earliest and latest P wave component, all ECGs were amplified at 40 mm/mV with a speed of 100 mm/s (Figure 7).

PWD and amplitude were measured using a digital caliper by two cardiologists blinded of stroke status of participants. In case of discrepancies in the results, a third cardiologist was asked to perform a control measurement.

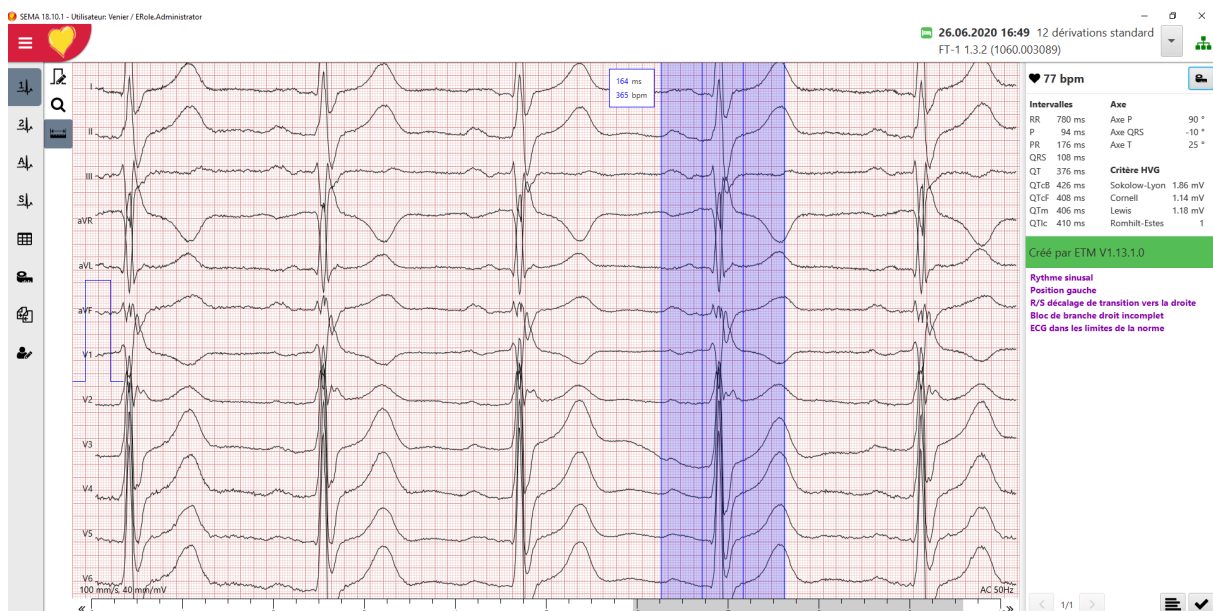


Figure 7 : SEMA software interface for amplified P-wave measurement. Note the IAB identifiable in lead DIII.

TTE measurements

Transthoracic echocardiography was performed for all participants using a General Electric Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway) equipped with a 2.5 MHz transducer and high frame rate (60 frames per second).

Images were digitally stored for offline analysis (EchoPAC, version 113 1.1, GE-Vingmed, Horten, Norway). A single echocardiographer blinded to stroke status conducted all echocardiographic examinations and analyzed echocardiographic parameters.

Regular echocardiographic parameters as left ventricular end diastolic diameter (LVEDD) left ventricular systolic diameter (LVESD) and thickness of the left ventricular wall both in systole and diastole were performed using M-mode in the parasternal long-axis view. Peak early (E-wave) and late (A-wave) diastolic left ventricle (LV) filling velocities, E-wave deceleration time, and E/A velocity ratios were determined using standard Doppler imaging.

Left ventricle ejection fraction (LVEF) was calculated using the Simpson's biplane method. Maximal left atrial (LA) volume was measured in apical four- and two-chamber views. We performed body surface area indexing for LAVs measurements using the Mosteller formula.

LA reservoir strain was evaluated using 2D speckle tracking on images obtained from the apical 4- and 2-chamber view in a semi-automatic process. Septal and lateral base and roof of the left atrium were marked manually.

The endocardial wall of the left atrium was then traced with an automatically adjusted thickness. Manual correction could be made in case of suspected poor tracking. Peak of R-wave was chosen for gating (R-R gating).

LA reservoir strain was measured as the peak global longitudinal strain (PGLS) during ventricular systole (*Supplementary files*). Conduit and contractile LA strain values were also collected (*Figure 8*).

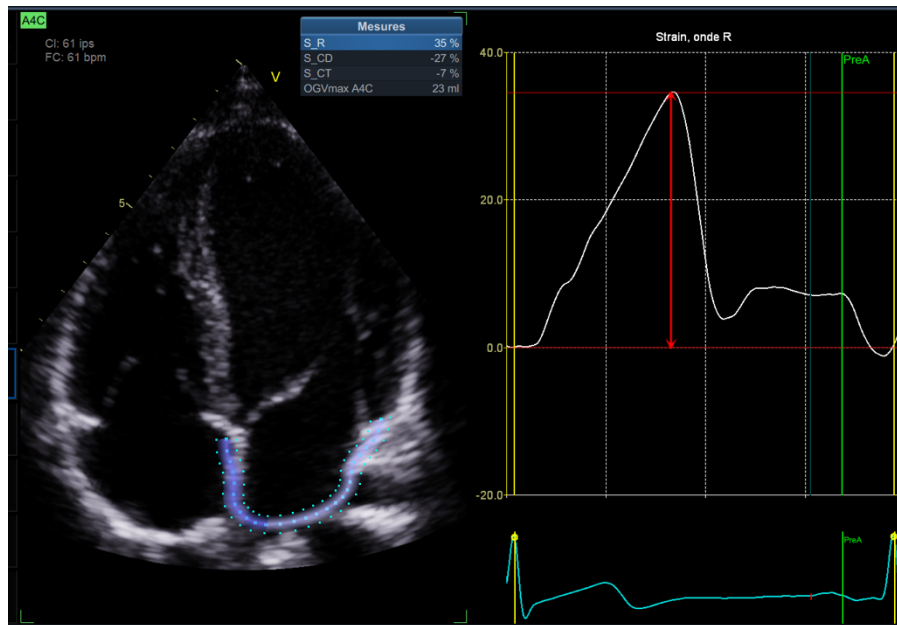


Figure 8 : 2D speckle tracking for determination of LA strain. SR = Strain reservoir ; SCd = Strain conduit ; SCT = Strain contractile.

Mechanical activation of the LA measured using color-coded tissue Doppler echocardiography (PA-TDI) was also collected in all patients included in the study.

This measurement was performed from a tissue Doppler imaging of the lateral wall of left atrium. PA-TDI duration was obtained by measuring the delay between the onset of the P wave on the surface ECG and the peak of the mitral tissue doppler A' wave (*Figure 9*).

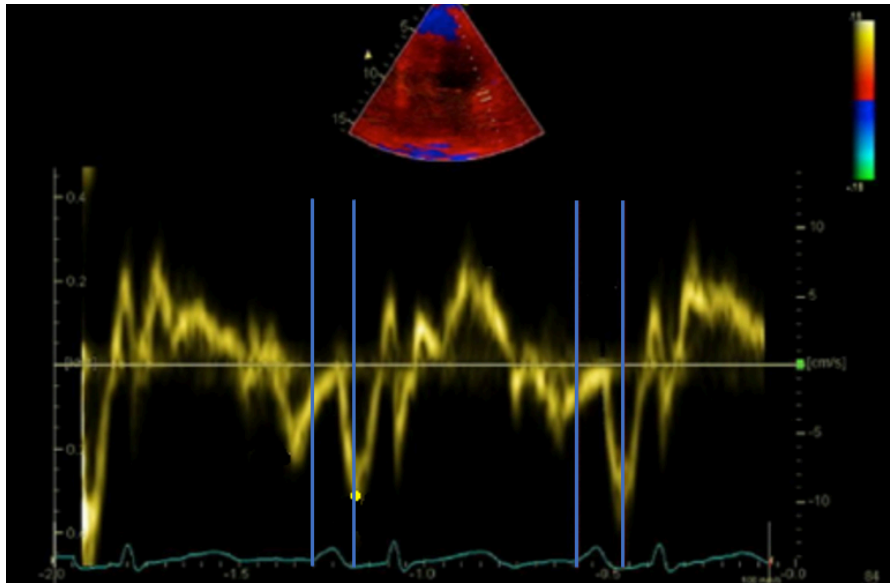


Figure 9 : Tissue doppler imaging of the atrial lateral wall. PA-TDI interval measurement

Follow up

All patients in stroke group have underwent implantation of an ILR (Reveal, Medtronic or Confirm RX, St Jude Medical) before enrollment. The device allowed telecommunication and all alerts were interpreted by cardiologists specialized in arrhythmias. AF was considered after an episode lasting more than 30 seconds.

Statistical analysis

Normal distribution of continuous variables was tested using a Shapiro-Wilk test when necessary. Mean values were compared using Student' t-test if all application conditions were verified. Kruskal-Wallis test was used to compare ranks otherwise. Results are presented as mean \pm standard deviation in case of normal distribution, and median with quartiles otherwise. Comparison of qualitative variables between groups was performed using Chi-square test or Fisher test. Multivariate analyses were performed using a model of

logistic regression. Potential adjustment variables were selected from the set of variables collected according to the literature and in such a way that there were less than 20% of patients with missing data or variables with less than 5% missing values.

The cutoff value of PWD for predicting increased risk of CS was determined by the receiver operating characteristic (ROC) curves with sensitivity on the y-axis and 1-specificity on the x-axis. Area under the curve (AUC) of the ROC was used to evaluate the diagnostic value of test performed : null (AUC = 0.5), poor informative (0.5 < AUC < 0.7), fairly informative (0.7 < AUC < 0.9), highly informative (0.9 < AUC < 1) and perfect (AUC = 1).

Correlation studies were performed to investigate the association between P wave duration and the other parameters. AF occurrence and stroke recurrence over time were plotted using a Kaplan Meier curve. Interrater reliability for PWD measures was determined used Lin's Concordance Coefficient Correlation (CCC) from logarithmic transformed variables.

A p-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS (*IBM SPSS Statistics Version 24*).

RESULTS

A total of 95 patients with CS and 96 controls were included. The average time between incident stroke and enrollment was 30 months.

Clinical data, TTE and ECG results of CS and controls are presented in *Table 2*. Groups were comparable on age, body mass index (BMI) and CHADS VASC score. There was a predominance of men in both groups.

85.3% of patients in CS group had image evidence of ischemic stroke and 15% had a neurological presentation compatible with TIA with normal imaging.

Patients in CS group were more often treated with antithrombotic drugs (antiplatelet agents or anticoagulants) and statins than controls.

Patients in the control group were referred mostly for preoperative assessment prior to extracardiac surgery (25%), cardiac evaluation following a Covid-19 infection or in diabetes mellitus condition (18 and 19% respectively), or for a stress test (18%).

Compared with controls, patients in stroke group had significantly increased P wave duration (133 ± 13 and 122 ± 15 ms respectively, $p < 0.001$) (*Figure 10*). The interrater reproducibility of the PWD measurement was good according to the Lin's CCC (> 0.70). No difference was found between groups regarding the P-wave automated device calculation.

Compared with controls, CS patients had a prolonged PA-TDI interval (136 ± 20.2 ms and 129 ± 18.8 ms respectively, $p = 0.029$). Patients in CS group had larger LAV indexed and LA surface than controls.

| Clinical characteristics | CS group (n = 95) | Controls (n=96) | p value |
|---|-------------------|-----------------|-------------------|
| Age (years) | 60.8 ± 12.5 | 57.3 ± 13.9 | 0,068 |
| Men | 53 (55%) | 61 (63.5%) | 0,275 |
| Body mass index (kg/m ²) | 26.4 ± 5.83 | 26.5 ± 5.51 | 0,841 |
| CHADS VASC score | 1.5 ± 1.17 | 1.8 ± 1.28 | 0,152 |
| Current smoker | 21 (22.1%) | 15 (15.6%) | 0,252 |
| Hypertension | 46 (48.4%) | 40 (42%) | 0,348 |
| Diabetes mellitus | 7 (7.4%) | 32 (33%) | < 0,001 |
| Dyslipidemiae | 26 (27.4%) | 37 (38.5%) | 0,101 |
| Carotid artery stenosis | 5 (5.3%) | 4 (4.2%) | 0,747 |
| Sleep apnea syndrome | 23 (34.8%) | 8 (10.8%) | < 0,001 |
| Beta-blocker | 13 (13.7%) | 23 (23.9%) | 0,069 |
| ACEi or ARB | 40 (42.1%) | 38 (39.6%) | 0,723 |
| Aspirin or Clopidogrel | 76 (80%) | 26 (27.1%) | < 0,001 |
| Anticoagulant | 21 (22.1%) | 6 (6.3%) | 0,002 |
| Statin | 62 (65.3%) | 36 (37.5%) | < 0,001 |
| Diuretic | 16 (16.8%) | 16 (16.7%) | 0,974 |
| PWD auto (ms) | 110 (±14.0) | 104 (±23.5) | 0.09 |
| PWD (ms) | 133 (±15.3) | 122 (±13.3) | <0.001 |
| Amplitude (mV) | 0.16 (±0.06) | 0.157 (±0.04) | 0.722 |
| PR (ms) | 161 (±32.3) | 159 (±23.6) | 0.712 |
| QRS (ms) | 91.7 (±11.5) | 90.4 (±11.8) | 0.444 |
| QTc (ms) | 426 (±21.8) | 427 (±28.9) | 0.8 |
| Left atrial anteroposterior diameter (mm) | 30.6 (±5.64) | 30.6 (±4.82) | 0.99 |
| E/E' | 5.94 (±2.41) | 6.52 (±1.99) | 0.092 |
| Heart rate (ppm) | 70.8 (±12.3) | 74.0 (±13.8) | 0.1 |
| LVEF (%) | 63.4 (±6.79) | 63.4 (±7.16) | 0,972 |
| LA surface (cm ²) | 18.6 (±3.90) | 17.2 (±3.56) | 0.024 |
| Conduit strain (%) | 13.8 (±5.55) | 16.6 (±7.35) | <0.01 |
| Reservoir strain (%) | 28.6 (±6.95) | 30.6 (±7.86) | 0.096 |
| Contractile strain (%) | 14.9 (±4.82) | 14.0 (±4.38) | 0.215 |
| PA-TDI (ms) | 136 (±20.2) | 129 (±18.8) | 0.029 |
| LA Volume indexed (ml/m ²) | 27.3 (±8.51) | 23.7 (±7.80) | <0.01 |

Table 2 : Clinical characteristics of CS stroke and controls. ACEi = Angiotensin converter enzyme inhibitor ; ARB = Angiotensin receptor blocker ; LA = Left atrium ; Left Ventricle Ejection Fraction ; PWD = P-wave duration ; TAPSE = Tricuspid annular plane systolic excursion.

CS patients had an impaired LA reservoir strain but not reaching the significance threshold.

In contrast, the conduit strain was significantly lower in the CS group compared with controls

(13.8 ± 7% and 16.6 ± 6% respectively, p < 0.01).

Predictive risk factors of CS

Results of multivariate logistic regression analysis for predictors of CS are shown in *Table 3*.

PWD (OR 1.07; 95% CI, 1.03; 1.09; $p < 0.001$) was significantly associated to stroke status. AF (OR 0.06; 95% CI, 0.01 ; 0.64; $p = 0.02$) and obstructive sleep apnea (OSA) syndrome (OR 0.29; 95% CI, 0.10; 0.08; $p = 0.02$) were also linked to CS status.

| Variable | Odds-Ratio (95% CI) | p |
|----------------|------------------------|------------------|
| PWD | 1.07 [1.03; 1.10] | <0.001 |
| AF | 0.06 [0.01; 0.64] | 0.02 |
| LVEF | 0.97 [0.91; 1.02] | 0.44 |
| CHADSVASC | 0.65 [0.46; 0.92] | 0.08 |
| Conduit strain | 0.94 [0.88; 1.01] | 0.07 |
| OSA | 0.29 [0.10; 0.08] | 0.02 |

Table 3 : Multivariate logistic regression analysis.; LA = left atrial ; TAPSE = tricuspid annular plane systolic excursion; PWD = P wave duration; OSA = Obstructive sleep apnea; AF=atrial fibrillation; LVEF=left ventricular ejection fraction

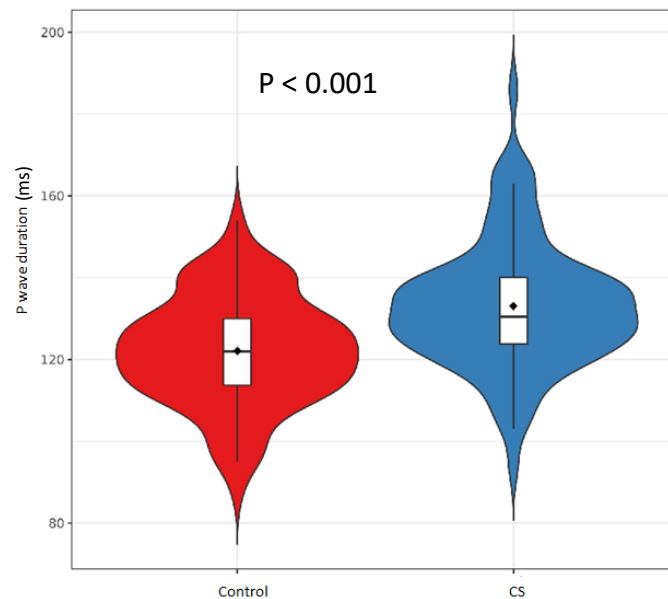


Figure 10 : P wave duration among groups. CS = Cryptogenic stroke

There was a linear relationship between PWD and LA surface ($r = 0,43$, $p < 0.001$) (Figure 11A) and PWD and conduit strain ($r = -0.27$, $p < 0.001$) (Figure 11B) in all patients.

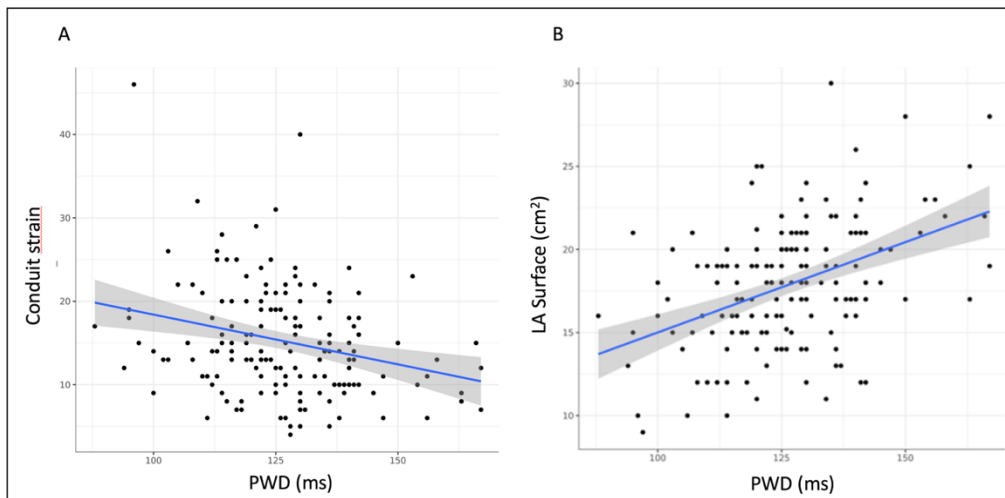


Figure 11 : Linear correlation between LA surface, conduit strain and PWD. PWD = P-wave duration; LA = Left atrial

Cutoff value of PWD for predicting risk of cryptogenic stroke

The AUC for PWD was 0.76 ($p < 0.001$) which was fairly informative for predicting an increased risk of cryptogenic stroke. The cutoff value of PWD was 135 ms (sensitivity, 64%; specificity 81%) (Figure 12).

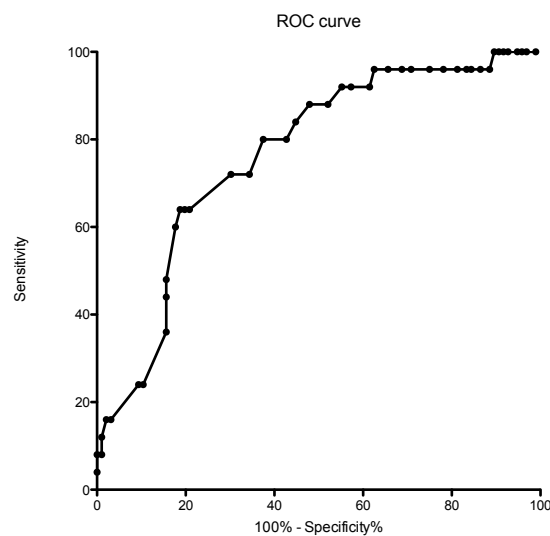


Figure 12 : The receiver operating characteristic (ROC) curve for PWD. The area under the curve was 0.76 ($p < 0.001$). PWD = P wave duration

Follow-up

The average time of monitoring with the ICM was 26 months. During follow-up, 11 patients (12%) developed AF, with a median time to occurrence of 460 days. The detection rates were 8% at 1 month and 16% at 6 months. 7 patients (7%) had recurrent stroke. No deaths were reported in either group during follow-up (*Figure 13*).

There was no significant difference on any of the variables studied between patients who developed AF and recurrent stroke or not.

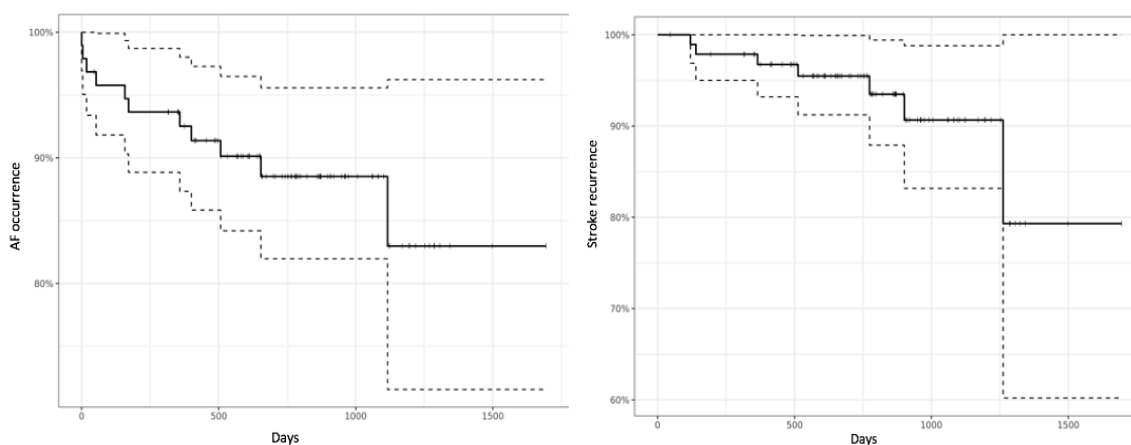


Figure 13 : AF occurrence and stroke recurrence during follow-up

Subgroup analysis in CS group according to brain imaging

Review of brain imaging revealed an occlusion of a proximal artery in 16% of patients.

10 patients in CS group had deep infarcts consistent with small vessel disease and 3 had significant ipsilateral atheroma. 18% of patients had multiple territory stroke and 25% had recent and older lesions.

Ischemic lesions were essentially cortical (*Table 4*). According to these points and clinical datas, a proposal of ASCOD classification was submitted in *Supplementary files*.

| Territory | n |
|--------------------------|----------|
| Subcortical | 18 (27%) |
| Cortical | 31 (47%) |
| Cortical and subcortical | 8 (12%) |
| Supra and infratentorial | 1 (2%) |
| Infratentorial | 8 (12%) |

Table 4 : Localization of the acute ischemic lesion. Supratentorial includes cerebral hemispheres and deep structures around the third ventricle ; Infratentorial includes brainstem and cerebellum

In CS group, patients with multiple lesions were significantly older (68.0 [62.0; 71.0] years and 57.0 [48.0; 65.2] years respectively, $p < 0.01$) and had a significantly longer PWD compared with the others (136 [127; 140] ms and 128 [122; 134] ms respectively, $p = 0.013$). There was also a prolonged E/E' ratio in CS with multiple territory while remaining within normal range (6.30 [5.53; 7.57] and 5.00 [3.95; 6.55] respectively, $p=0.026$) (Table 4).

| | No multiple territory/ Older and recent ischemic lesion (n = 40) | Multiple territory/ Older and recent ischemic lesion (n = 26) | p |
|---|--|---|-----------------|
| Age (years) | 57.0 [48.0; 65.2] | 68.0 [62.0; 71.0] | <0.01 |
| Left atrial anteroposterior diameter (mm) | 31.0 [28.0; 34.0] | 29.5 [24.8; 36.2] | 0.8 |
| E/E' | 5.00 [3.95; 6.55] | 6.30 [5.53; 7.57] | 0.026 |
| Heart rate (ppm) | 71.7 [60.0; 80.4] | 69.8 [64.7; 74.0] | 0.34 |
| LVEF (%) | 58.0 [54.2; 65.8] | 61.5 [53.8; 65.0] | 0.73 |
| BMI (kg/m ²) | 25.3 [23.1; 27.7] | 24.7 [20.8; 29.3] | 0.46 |
| PWD (ms) | 128 [122; 134] | 136 [127; 140] | 0.013 |
| Left atrial surface (cm ²) | 19.0 [15.6; 20.5] | 19.0 [15.8; 22.0] | 0.39 |
| Strain conduit (%) | 13.0 [10.0; 20.0] | 14.0 [12.0; 16.0] | 0.88 |
| Strain reservoir (%) | 31.0 [23.0; 35.0] | 28.0 [24.0; 36.0] | 0.75 |
| PA-TDI (ms) | 141 [132; 151] | 139 [128; 151] | 0.66 |
| Atrial fibrillation | 7 (18%) | 2 (7.7%) | 0.46 |
| Hypertension | 15 (38%) | 14 (54%) | 0.19 |

Table 3 : Comparison of CS according to the presence of multiple territory/older and recent lesion

DISCUSSION

This study found a significant prolongation of PWD in patients with CS compared to stroke-free participants. We found a linear relationship between PWD and LA surface and conduit strain in all participants.

CS remains a challenge due to the lack of existing specific recommendations on its diagnostic or therapeutic management.

In recent years, the concept of embolic stroke of undetermined source (ESUS) has been developed, based on the hypothesis that a large number of these CS have a cardioembolic origin by argument of frequency (26). It is characterized by specific clinical and imaging criteria. With this definition, large randomized trials have been conducted to study use of curative anticoagulation rather than antiplatelet therapy in this population with negative results (27,28). This suggests that the definition of ESUS is still too blurred and does not allow discrimination of patients who are effectively at high embolic risk.

On the other hand, AF seems to be a leading cause of CS with detection rates significantly improved by the use of ILR. However, recent studies suggest that AF may be a simple marker of atrial dysfunction, and not a prerequisite for stroke occurrence. Indeed, it has been demonstrated that nearly 65% of patients with CS have atrial cardiopathy (17). Considering that AF is usually found in 30% of cases, this suggests that nearly 35% of strokes have atrial dysfunction without AF.

Several markers of atrial function have been studied, but the difficulty is that these markers are not specific for atrial dysfunction and may be found in many different diseases (16).

It is therefore crucial to identify which marker seems to be the most relevant to screen high embolic risk patient. We found a significant prolongation of PWD in patients with CS

compared with controls. This result was consistent with prior studies which showed that an increased PWD was correlated with presence of left atrial fibrosis in magnetic resonance imaging (MRI). This highlights the value of ECG analysis among patients with CS in sinus rhythm. Indeed, PWD measurement is a tool readily available in routine as all patients have repeated ECGs during their hospitalization in the acute phase. Furthermore, most patients do not undergo TTE before hospital discharge. This parameter could help to identify patients at high embolic risk and guide antithrombotic management. We used a high amplification approach to improve our calculations. In fact, there was no significant difference in the automatic measurement of the P-wave duration reported by the device, whereas we demonstrated a significant difference. This supports the relevance of this technique, which can be easily performed in clinical practice after a slight learning curve.

We identified a linear relationship between PWD and LA surface in all participants. LA surface is an important predictor of AF and stroke occurrence (29). However, it has been shown that it is not a very sensitive marker to detect minimal impairments in atrial function, and interatrial block may be present without related LA enlargement (24,30).

In our study, 11 patients experienced AF, which represents a detection rate of 12% with ICM. These results are lower than those found in CRYSTAL-AF, which reported a detection rate of 30% (9). This may be explained by the fact that we excluded elderly patients over 80 years, although AF is known to affect this population in particular. Moreover, the mean time from the acute ischemic stroke to implantation of ILR was 397 days, whereas the highest AF detection rates are reported in the first 3 months after stroke.

On the other hand, the median duration of AF occurrence was > 1 year in our study, reinforcing the hypothesis that AF is not a precondition for stroke but potentially a simple

marker of atrial dysfunction. It is interesting to note that only 27% of the patients who developed AF were previously treated with anticoagulants at post-stroke hospital discharge. OSA syndrome and AF occurrence were also statistically associated with CS status. This result should be interpreted with some caution considering the differences in AF and sleep apnea diagnosis approach between groups.

In our study, LA reservoir strain appeared to be lower in CS patients without achieving significance. LA reservoir strain has been shown to inversely correlate with LA fibrosis burden demonstrated on late gadolinium contrast enhanced cardiac magnetic resonance (31). There are several methods for assessment of left atrial strain with results that may differ depending on the parameters (32). We chose R-R gating as recommended by a recent EACVI consensus (33), contrast with some studies that used P-P gating.

One of the strengths of this study is the use of a dedicated software for LA strain with good intra-observer reproducibility. In fact, most of the studies previously published have used software originally developed for the left ventricle with a ROI width and a division into twelve segments not suitable for the left atrium.

Our study revealed that there was an impairment of the conduit strain in patients with cryptogenic stroke compared with controls and a linear relationship between PWD and LA conduit strain among all participants. There are currently insufficient data in the literature regarding this outcome.

PA-TDI interval was significantly increased in CS patients. Our study was not powered to support this result after adjustment. PA-TDI duration on tissue doppler imaging measures the total atrial activation time and is a noninvasive method of assessing atrial fibrosis (34).

Further randomized studies will be necessary to validate these results and develop an algorithm encompassing different markers to target patients at high embolic stroke risk who will be offered armed surveillance and specific therapeutic management.

Study limitations

Our study has several limitations that should be mentioned.

First, we included a small number of patients making interpretation of subgroup analyses difficult.

Among controls, there was a population selection bias with a considerable number of patients with diabetes. Diabetes mellitus is known to cause heart failure with preserved ejection fraction (HFpEF) over time and a strong association between LA reservoir strain and diastolic dysfunction has been demonstrated (35,36). This could explain why we were unable to find a significant difference in the LA strain reservoir between our groups.

Finally, OSA is routinely investigated in stroke patients compared to the general population. Also, AF was diagnosed by the ILR in the CS group whereas controls didn't have a continuous monitoring. All these reasons could therefore constitute a bias in the analyses.

CONCLUSION

Amplified P-wave duration is prolonged in patients with cryptogenic stroke compared with a stroke-free control group. This study is the first to our knowledge to have compared P-wave duration using a simple and reproducible ECG amplification method in a population of patients with cryptogenic stroke versus a stroke-free control group.

Future studies will be required to determine the most effective algorithm for stratification of embolic risk and to compare different antithrombotic strategies in this population.

THÈSE SOUTENUE PAR : Elodie DESCHAMPS

TITRE :

DUREE DE L'ONDE P DANS L'ACCIDENT VASCULAIRE CEREBRAL CRYPTOGENIQUE : UNE ETUDE CAS-TEMOIN PROSPECTIVE.

CONCLUSION :

L'accident vasculaire cérébral (AVC) cryptogénique représente jusqu'à 30% des AVC et constitue un challenge en termes de prévention secondaire du fait de l'absence de cause identifiée.

Même si le diagnostic de fibrillation auriculaire (FA) a augmenté dans cette population du fait du développement du holter implantable sous cutané, elle ne serait pas une condition indispensable à la survenue de l'AVC mais plutôt un marqueur de dysfonction atriale.

De nombreux travaux ont été menés afin de mettre en évidence des marqueurs de dysfonction atriale et évaluer leurs valeurs pronostiques mais avec des résultats qui n'ont pas été validés dans des essais randomisés.

Cette étude est la première à notre connaissance à avoir comparé la durée de l'onde P en utilisant une méthode simple et reproductible d'amplification de l'ECG, chez une population de patients ayant présenté un AVC cryptogénique par rapport à un groupe témoin indemne d'AVC.

95 patients ont été inclus dans le groupe AVC et 96 sujets dans le groupe contrôle. La mesure de la durée de l'onde P a été réalisée chez tous les participants. Nous avons également évalué l'amplitude et la morphologie de l'onde P, ainsi que plusieurs paramètres échographiques (strain de l'oreillette gauche, surface de l'oreillette gauche) afin d'évaluer leurs corrélations avec l'onde P. Les patients du groupe AVC étaient tous porteurs d'un holter implantable avec système de télécardiologie permettant la détection de FA pendant toute la durée du suivi.

La durée de l'onde P était significativement allongée chez les patients du groupe AVC par rapport aux témoins (133 ± 13 et 122 ± 15 ms respectivement, $p < 0.001$). Ce résultat persistait après ajustement sur les facteurs confondants. La durée de l'onde P et la surface de l'oreillette gauche étaient corrélées, ce qui signifie qu'un allongement de l'onde P était associé à une taille de l'oreillette gauche plus importante ($r = 0,43$, $p < 0.001$).

Pendant la durée du suivi, 11 patients (12%) ont présenté de la FA et 7 patients (7%) ont eu une récurrence d'AVC. Il n'existait pas de différence significative sur les variables étudiées entre ceux qui ont présenté de la FA ou une récurrence d'AVC et les autres. Les patients présentant des lésions ischémiques dans des territoires multiples ou d'âges différents avaient une durée de l'onde P significativement allongée par rapport aux autres (136 ms [127 ; 140] et 128 ms [122 ; 134] respectivement, $p = 0.013$).

La durée de l'onde P est un marqueur de dysfonction atriale facilement réalisable en pratique clinique qui pourrait entrer dans l'algorithme de prise en charge thérapeutique des patients victimes d'un AVC cryptogénique.

VU ET PERMIS D'IMPRIMER
Grenoble, le :

LE DOYEN

Doyen de l'UFR de Médecine

Pr. Patrice MORAND

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LE PRÉSIDENT DE LA THÈSE

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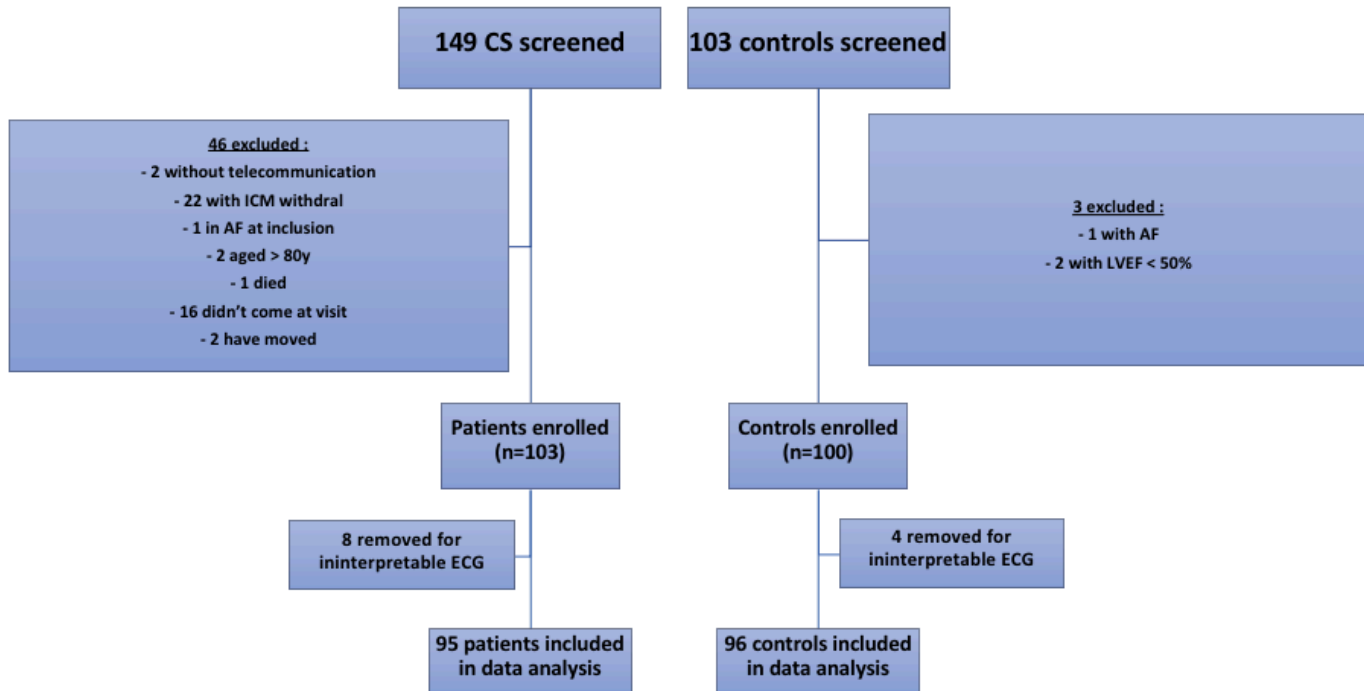
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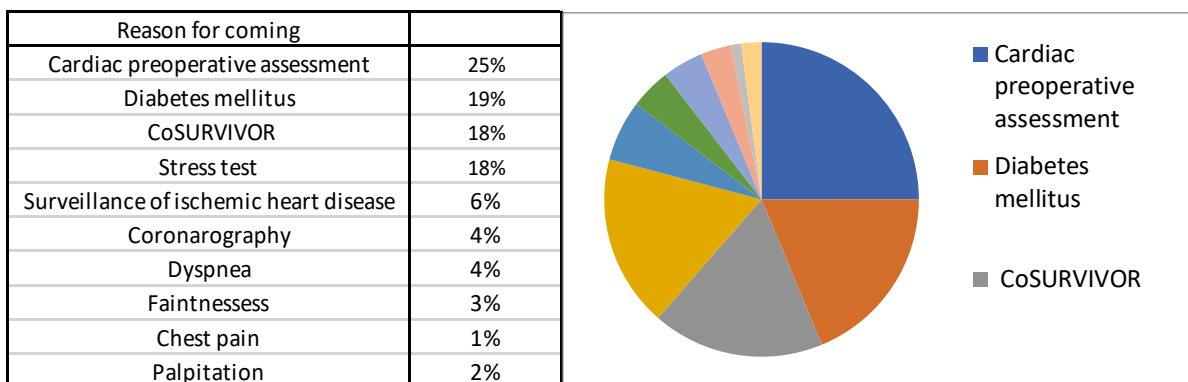
Supplementary files

○ Inclusion flow-chart for cases and controls



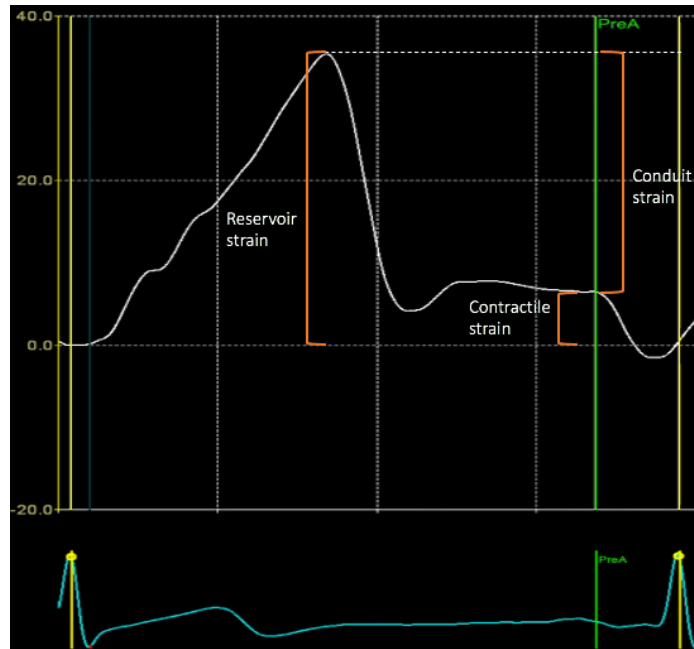
CS = Cryptogenic stroke ; ICM = Insertable cardiac monitor ; AF = Atrial fibrillation ; ECG = Electrocardiogram ; LVEF = Left ventricular ejection fraction

○ Reason for consult among controls



- **Left atrial strain principle**

Strain was initially developed to provide a quantitative assessment of left ventricular function. The myocardial strain corresponds to the deformation of the myocardium from its baseline form and the strain rate to the deformation rate. It can be performed using velocities acquired by tissue doppler imaging or by 2D speckle tracking. 2D speckle tracking is based on tracking of acoustic markers naturally present in the myocardial wall. This latter has the advantage of being angle-independent. It is thus possible to determine the LA reservoir strain (or global strain), which corresponds to the blood storage during ventricular systole; LA conduit strain which corresponds to passive blood flow from the atrium to the ventricle; and contractile strain which corresponds to active emptying by contraction of the atrium.



Illustrations of LA strain curve

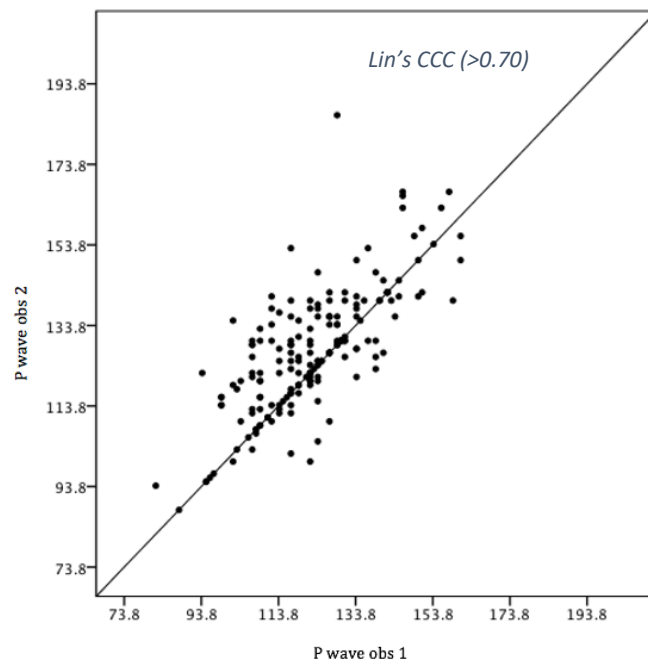
○ **Infarct location and ASCOD classification among CS group**

| Case n° | Age (y) | Sexe | Location | A-S-C-O-D classification |
|----------------|----------------|-------------|--------------------------|---------------------------------|
| 3 | 65 | male | subcortical | A0-S0-C9-O0-D0 |
| 4 | 56 | female | subcortical | A0-S2-C9-O0-D0 |
| 5 | 71 | male | infratentorial | A0-S0-C2-O0-D0 |
| 7 | 61 | male | cortical | A0-S0-C9-O0-D0 |
| 8 | 73 | female | subcortical | A0-S0-C2-O0-D0 |
| 10 | 66 | male | infratentorial | A0-S0-C9-O0-D0 |
| 12 | 80 | female | subcortical | A0-S0-C2-O0-D0 |
| 13 | 22 | male | cortical | A0-S0-C9-O0-D0 |
| 15 | 57 | male | subcortical | A0-S0-C2-O0-D0 |
| 16 | 48 | male | cortical and subcortical | A0-S0-C9-O0-D0 |
| 17 | 73 | female | subcortical | A0-S0-C2-O0-D0 |
| 18 | 73 | female | infratentorial | A0-S0-C9-O0-D0 |
| 19 | 71 | female | subcortical | A0-S2-C9-O0-D0 |
| 22 | 59 | male | cortical and subcortical | A0-S0-C9-O1-D0 |
| 24 | 42 | female | cortical | A0-S0-C2-O0-D0 |
| 26 | 69 | male | infratentorial | A0-S0-C9-O0-D0 |
| 27 | 69 | female | cortical | A0-S0-C2-O0-D0 |
| 28 | 68 | male | cortical | A0-S0-C2-O0-D0 |
| 31 | 50 | female | cortical | A0-S0-C9-O0-D0 |
| 32 | 75 | female | cortical | A0-S0-C9-O0-D0 |
| 33 | 78 | female | cortical | A0-S0-C9-O0-D0 |
| 34 | 69 | male | cortical | A0-S0-C2-O0-D0 |
| 36 | 62 | male | cortical | A0-S1-C2-O0-D0 |
| 38 | 53 | male | cortical and subcortical | A1-S0-C9-O0-D0 |
| 40 | 63 | male | cortical | A0-S0-C9-O0-D0 |
| 42 | 71 | female | cortical | A0-S0-C2-O0-D0 |
| 44 | 57 | male | subcortical | A1-S0-C9-O0-D0 |
| 45 | 68 | male | cortical and subcortical | A0-S0-C2-O0-D0 |
| 46 | 62 | female | cortical | A0-S0-C2-O0-D0 |
| 47 | 48 | female | infratentorial | AC-S0-C9-O0-D0 |
| 48 | 45 | female | cortical and subcortical | A0-S0-C9-O0-D0 |
| 49 | 58 | male | cortical | A0-S0-C9-O0-D0 |
| 50 | 59 | male | cortical and subcortical | A0-S0-C9-O0-D0 |
| 51 | 57 | male | cortical | A0-S0-C9-O0-D0 |
| 53 | 44 | male | cortical and subcortical | A0-S0-C9-O0-D0 |
| 54 | 59 | female | cortical | A0-S0-C2-O0-D0 |
| 56 | 49 | female | cortical | A0-S0-C9-O0-D0 |
| 57 | 70 | female | subcortical | A0-S0-C2-O0-D0 |
| 58 | 37 | male | subcortical | A0-S0-C9-O0-D0 |
| 59 | 71 | female | cortical | A0-S0-C2-O0-D0 |
| 60 | 31 | male | cortical | A0-S0-C9-O0-D0 |
| 61 | 48 | female | subcortical | A0-S0-C9-O0-D0 |

(Continued)

| Case n° | Age (y) | Sexe | Location | A-S-C-O-D classification |
|----------------|----------------|-------------|--------------------------|---------------------------------|
| 62 | 46 | male | cortical and subcortical | A0-S0-C2-O0-D0 |
| 64 | 70 | male | cortical | A0-S0-C2-O0-D0 |
| 65 | 57 | male | subcortical | A1-S0-C9-O0-D0 |
| 67 | 68 | female | cortical | A0-S3-C2-O0-D0 |
| 68 | 66 | male | supra and infratentorial | A0-S0-C2-O0-D0 |
| 69 | 66 | male | cortical | A0-S0-C2-O0-D0 |
| 70 | 74 | male | subcortical | A0-S2-C2-O0-D0 |
| 71 | 73 | male | cortical | A0-S0-C9-O0-D0 |
| 73 | 74 | female | subcortical | A0-S0-C9-O0-D0 |
| 75 | 48 | female | subcortical | A0-S0-C9-O0-D0 |
| 76 | 42 | male | cortical | A0-S0-C2-O0-D0 |
| 77 | 42 | female | infratentorial | A0-S0-C9-O0-D0 |
| 78 | 20 | male | cortical | A0-S0-C9-O0-D0 |
| 79 | 64 | female | infratentorial | A0-S0-C2-O0-D0 |
| 80 | 65 | female | cortical | A0-S0-C2-O0-D0 |
| 84 | 57 | male | cortical | A0-S0-C9-O0-D0 |
| 85 | 48 | male | cortical | A0-S0-C9-O0-D0 |
| 86 | 50 | female | cortical | A0-S0-C2-O0-D0 |
| 87 | 51 | female | infratentorial | A0-S0-C9-O0-D0 |
| 89 | 39 | male | cortical | A0-S0-C9-O0-D0 |
| 90 | 76 | female | subcortical | A0-S1-C2-O0-D0 |
| 91 | 46 | male | cortical | A0-S0-C2-O0-D0 |
| 92 | 68 | male | subcortical | A0-S1-C9-O0-D0 |
| 95 | 63 | male | subcortical | A0-S0-C2-O0-D0 |

- **Interrater reproducibility of the PWD**



Le serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. ”