

Association between heart and dementia... keep an eye on the left atrium

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Atrial fibrillation is associated with an increased risk of cognitive impairment and dementia. The mechanisms are not well known, but they are probably multifactorial and involve atrial myopathy, cardio-embolism, cerebral hypoperfusion, and comorbidities (systemic vascular sclerosis, disease of the small cerebral vessels, inflammation, etc.). Atrial fibrillation therapy could have a protective effect on dementia through diversified actions: (i) prevention of left atrial remodelling; (ii) prevention of cardio-embolism and silent (and not) cerebral infarcts; (iii) improvement of cardiac output and cerebral perfusion. Randomized trials will be needed to clarify the links between left atrium and dementia and to identify the most appropriate therapeutic strategies.

Introduction

Scientific evidence suggests that atrial fibrillation may be a crucial element in the progression of cognitive impairment and dementia. The association is only partially explained by shared risk factors and by the chance coexistence of both diseases with advancing age. The best-known mechanism is the cognitive impairment that follows a cardio-embolic stroke, a phenomenon described in 33% of strokes at 5 years. However, the relationship between atrial fibrillation and dementia is much more complex and multifactorial, observed with high frequency even in patients with no history of stroke or TIAs (transient ischaemic attack). Some reflections suggest that cardio-embolism is not the only possible explanation of the link between atrial arrhythmias and dementia. In short: (i) the temporal relationship between atrial fibrillation and ischaemic stroke is often non-existent and today it is thought that the atrium itself can provide an embolic prone environment even in the absence of arrhythmia (so-called atrial cardiomyopathy), (ii) as far as it is theoretically possible that atrial fibrillation may be the cause of small, clinically silent cerebral embolisms, arrhythmia can alter cerebral flow with different

mechanisms, notably hypoperfusion due to reduced cardiac output or beat-to-beat flow variation, (iii) furthermore, atrial fibrillation can be a marker and not a cause of neurological damage, through the association with vascular sclerosis and/or systemic inflammation, conditions that can result in cerebral vascular damage and in progressive alterations of cognitive processes. It can therefore be summarized that the mechanisms that link atrial fibrillation to dementia are not clear and may involve various phenomena, such as cerebral micro-infarcts, cerebral hypoperfusion, micro-haemorrhages, inflammation, as well as cerebral atrophy and systemic atherosclerosis.

Cardio-embolism and dementia

The risk of dementia approximately doubles in patients with atrial fibrillation and remains elevated at about 40% even in cases with no history of stroke or TIA. Cognitive impairment is thought to be the result of a single critical stroke, multiple small brain infarcts, or secondary neuro-degeneration. Furthermore, atrial fibrillation is associated not only with cognitive decline, but also with a reduction in brain volume, all the more evident the more extensive the arrhythmia burden. Surprisingly, silent cerebral infarcts are five times more

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common than clinically evident forms. It follows that it is plausible that arrhythmia can cause progressive neuronal damage (and hence dementia) through repeated cerebral micro-embolisms and therefore subclinical micro-infarcts. The hypothesis is supported by a series of observations: (i) silent cerebral infarcts on MRI are described with high frequency in atrial fibrillation¹; (ii) silent cerebral infarcts are associated with dementia; (iii) microscopic brain damage, beyond resolution of traditional neuroimaging, correlate with cognitive dysfunction.² Although silent cerebral infarcts cause more limited brain damage than clinical stroke, the effects on cognitive impairment can be similar (this is not surprising considering that silent cerebral infarcts tend to be multiple and repetitive, so the damage is cumulative in the time). It must also be considered that atrial fibrillation is often associated with a disease of the small cerebral vessels, which can act synergistically on cognitive decline.

Alterations in cerebral perfusion and dementia

The brain is an organ with high metabolic demands, particularly sensitive to disturbances in blood flow and the availability of O₂. In physiological conditions, the self-regulation of the flow ensures correct perfusion of the brain tissue for a wide range of systemic pressures. In synchrony with self-regulation, the blood brain barrier regulates metabolic exchanges between bloodstream and nervous tissue, dynamically responding to changes in flow, oxidative stress, and the action of pro-inflammatory cytokines. Some speculate that the reduction in cerebral flow may be the cause of chronic hypoxemia and trigger a cascade of ischaemia-induced molecular events that would eventually lead to vascular dementia. In particular, in atrial fibrillation the cerebral flow (and therefore the shear stress) is altered both for a relative reduction of the cardiac output and for a beat-to-beat variation of the output.

Endothelial function and the integrity of the blood brain barrier are compromised by abnormal pulsatility and instantaneous changes in flow, even in the absence of cerebral ischaemic events. Cerebral hypoperfusion is accompanied by a reduction in grey matter and white matter, directly proportional to the arrhythmic burden.³ Brain flow, on the other hand, improves with the restoration of post-cardioversion sinus rhythm. Add to this the inflammatory state that often accompanies arrhythmia, to take into account how atrial fibrillation can compromise the blood brain barrier and cause chronic neurological damage. Furthermore, an anomaly in the permeability of the blood brain barrier can alter clearance and favour the accumulation of beta-amyloid protein, a distinctive feature of Alzheimer's disease. This would explain why atrial fibrillation increases the risk of all types of dementia, including Alzheimer's. In addition, brain damage can be amplified in the presence of other damaging factors of the blood brain barrier, such as age, arterial hypertension, diabetes, etc. Specifically, age and disease of the small cerebral vessels can alter the delicate mechanisms of self-regulation of flow thus putting the brain at risk. According to this hypothesis, typical markers of small cerebral vessel

disease (subcortical infarcts of limited extent, lacunae, micro-bleeds, and cerebral atrophy) are frequently described on MRI in patients with atrial fibrillation.

Atrial myopathy and dementia

Under normal conditions, the intra-atrial flow is swirling and at high speed, so as to ensure effective washing of the chamber in general and of the auricle in particular. Spartera *et al.*⁴ demonstrated that in the absence of atrial fibrillation (or before the arrhythmia appears) the flow rate and the vorticity index in the atrium are significantly reduced in subjects at high risk of stroke (i.e. those with elevated CHA₂DS₂-VASc). This data points towards the hypothesis of atrial myopathy as the underlying cause of cerebral cardio-embolism, even before atrial fibrillation. The arrhythmia would be a consequence of atrial myopathy, although there is no doubt that the electrical irregularity can accelerate the atrial pathology. In other words, atrial fibrillation would be both a marker of thrombogenic atrium and a cause of thromboembolism and cognitive impairment at the same time. Confirming this interpretation in the work of Spartera *et al.* the flow velocity and the vorticity index further decrease with the onset of arrhythmia.⁴ Multiple studies suggest that an alteration of the anatomy and/or function of the atrium, indicative of atrial myopathy, may be the cause of dementia regardless of atrial fibrillation. Several electrocardiographic markers of left atrium abnormality or atrial myopathy are correlated with a higher frequency of cognitive impairment. Bayes del Luna described a relationship between advanced inter-atrial block and the risk of dementia and mortality (*P* wave > 120 msec and morphology + - in D3).⁵ Gutierrez *et al.* in the ARIC-NCS Study observed that the *P* wave abnormality indices (especially the negative terminal forces in V1) correlate with dementia (+ 60%) regardless of stroke and atrial fibrillation.⁶ Furthermore, in an elderly community, frequent atrial extrasystoli were associated with cognitive impairment and a higher prevalence of dementia regardless of stroke history.⁷ These data support the concept that atrial cardiomyopathy *per se* may be responsible for brain events, through altered cardiac output and cerebral flow and/or subclinical cerebral micro-embolisms.

However, it remains to be clarified whether the relationship between atrial myopathy and dementia is mediated or not (and to what extent) by the onset of atrial fibrillation. In this regard, the connections between echocardiographic markers and brain deterioration appear interesting. Reduced indexes of left atrium 'reservoirs' are associated with silent cerebral infarcts and hyperintensity of the white matter.⁸ More recently, Wang verified the problem in the ARIC Study, on 4696 patients without cognitive alterations, followed prospectively for 6 years by evaluating the echographic basal indices of atrial function.⁹ The incidence of dementia was significantly increased in the quintile with more compromised indices (RR 1.98 for the 'reservoir strain', RR 1.50 for the 'conduit strain', RR 1.57 for the 'contractile strain', RR 1.8 for the 'emptying fraction', and RR 1.43 for the 'active emptying fraction').⁹

The authors conclude that there is a close relationship between atrial dysfunction and subsequent risk of dementia, unexplained (or only minimally explained) by a diagnosis of intercurrent atrial fibrillation. If these data will be confirmed in prospective randomized studies, it would follow that in cases of atrial myopathy an early anti-remodelling therapy could be useful to prevent dementia, even before the onset of atrial fibrillation.

Atrial fibrillation therapy and dementia

The role of anticoagulants

Based on the above considerations, it would be expected that anticoagulant therapy and/or rhythm control could have positive effects on the risk of dementia. In agreement with this hypothesis, observational studies suggest a protective effect of oral anticoagulant therapy (TAO) on the cognitive outcomes of atrial fibrillation. The results of vitamin K inhibitors would seem to be closely linked to the quality of treatment, assessed on the basis of time in therapeutic range (TTR): compared to an optimal therapy (mean TTR > 75%) the risk of dementia progressively increases as the TTR decreases (RR 2.5 for TTR between 51% and 75%; RR 4.10 for TTR 26% and 50%; RR 5.3 for TTR < 25%).¹⁰

These data are confirmed by the Olmestad County Population Based Study, where warfarin reduces the incidence of dementia by 20%, limited to the two quartiles with the highest TTR (RR 0.80, CI 0.64-0.99, $P < 0.05$). More recently, a lower risk of dementia and stroke has been suggested in patients treated with direct anticoagulants (DOAC) compared to warfarin. The superiority of DOACs compared to vitamin K inhibitors could be linked to the lower risk of cerebral haemorrhage and micro-bleeds, as well as to the efficacy in the prevention of ischaemic cerebral infarcts (in particular the clinically silent forms which, as mentioned, are more frequent and have a more subtle course). In contrast, European studies have found no significant difference between DOAC and Warfarin on the risk of dementia.^{11,12} Overall, the data on the subject are weak and conflicting and do not allow us to affirm with certainty the advantage of DOACs over warfarin or the usefulness of TAO on the prevention of cognitive impairment. One of the reasons is that OAT could promote damage from micro-bleeding, at least partially nullifying the advantages in terms of prevention of cardio-embolism. Second, it is possible that OAT is less effective in preventing micro-embolism and silent heart attacks than in clinical stroke. This interpretation is suggested by Kuhne who, in patients correctly treated with anticoagulants, after 2 years observed new cerebral infarcts (almost always silent) in 5.5% of cases, new white matter lesions in 18.7% and new 'micro-bleeds'. 'In 11.4%.¹³ In addition, patients with new brain infarcts showed greater decline in cognitive function. Overall, these data suggest that OAT may not be sufficient to prevent cerebral vascular damage. At the moment, it is not possible to say whether higher doses of the drug or the combination with antiplatelet agents may be more effective.

The role of rhythm control

It is not clear whether rhythm control in atrial fibrillation can have protective effects on the incidence of dementia. In theory, persistent sinus rhythm could reduce the risk of cerebral micro-embolisms and/or improve cardiac output and cerebral flow. On the one hand, a substudy of the AFFIRM found no significant differences between rhythm or rate control strategy; on the other hand, Lin describes an advantage of rhythm control in terms of dementia (-25%), especially in association with ASA and anticoagulants ($P < 0.03$).¹⁴ Furthermore, Kim notes, in patients treated with anticoagulants, that the rhythm control with drugs and/or ablation reduces the risk of dementia by 14%,¹⁵ especially in relatively young subjects with low CHA2DS2-VASc.

The role of trans-catheter ablation

Trans-catheter ablation could be the winning strategy, since it guarantees a more effective and lasting restoration of sinus rhythm than antiarrhythmic drugs. In support of this hypothesis, several observational studies suggest a cognitive improvement after ablation of the arrhythmia.¹⁶ However, it must be considered that ablation is associated with an increased risk of brain emboli, particularly in the immediate post-procedure period, which could nullify the positive effects of the procedure and paradoxically compromise cognitive functions. This mechanism would be operational especially in the first three months post-ablation, when the probability of damage to the atrial wall caused by the energy delivered by the scalor catheter is maximum. This would explain why early data on cognitive function within three months of the procedure are uncertain and inconclusive. The advantages of ablation and prolonged restoration of sinus rhythm could emerge later, both in terms of prevention of intra-atrial flow disturbances (reduction of cardio-embolism), and in terms of normalization of cardiac output (improvement of cerebral flow and protection of the blood brain barrier). In contrast to this hypothesis, the data on cognitive function from the CABANA and CASTLE-AF studies did not show significant differences 12 months after ablation.

However, cognitive impairment is a slow process that takes years, so 12 months of observation may be too short. In this regard, there are several reports that indicate a lower risk of dementia after ablation compared to medical therapy with a persistent advantage even after 9 years of follow-up.¹⁷ Currently, some studies suggest that post-ablation arrhythmic relapses are associated with greater cognitive impairment.¹⁶ It is also interesting to note that Bodagh¹⁸ described an improvement in brain function after ablation especially in Alzheimer's disease, even more so than in classical dementia. As previously mentioned, cerebral hypoperfusion can exacerbate beta-amyloid neuropathy, both due to increased enzyme production and reduced clearance of the protein from the brain. Ablation could effectively resolve cerebral hypoperfusion in Alzheimer's, while vascular dementia may not derive the same benefit due to the association between ablation and cerebral micro-emboli (at least in the first months post-procedure).

However, it remains to be defined whether post-ablation micro-emboli have the same meaning as the classical ones of atrial fibrillation, in terms of silent cerebral micro-infarcts and risk of dementia. In this regard, Kato¹⁹ observed a very high percentage of post-ablation embolic cerebral micro-infarcts (over 80-85% on high definition MRI), but surprisingly the damage regressed in a good number of cases at 6 months, probably due to the development of effective collateral circles. Most interestingly, these patients' overall brain functions improved significantly, despite brain damage on MRI. The concomitant improvement in ejection fraction, atrial volume, and pro-BNP suggests that the positive effect on cognitive abilities was linked to an increase in cardiac output and cerebral perfusion. To clarify the problem, prospective randomized studies are needed, which enroll patients without baseline cognitive alterations in order to correctly study the relationship between ablation and the incidence of dementia.

Mohanty recently compared oral anticoagulation therapy with auricle closure after a trans-catheter ablation procedure.²⁰ Cognitive impairment was observed in 55% of cases in OAT, while cognitive abilities remained normal in 91% of patients undergoing auricle occlusion.²⁰ On the one hand, it is confirmed that anticoagulant drugs are probably insufficient to prevent dementia; on the other hand, it is suggested that trans-catheter ablation enhanced by auricle occlusion (i.e. the association between optimal rhythm control and cardio-embolism control) could be the most complete and effective strategy for the prevention of cognitive impairment.

Conclusions

There are close relationships between the left atrium and the development of dementia. Brain damage can result from complex and in some ways undefined mechanisms, involving atrial myopathy, cerebral thrombo-embolism (silent or not), alterations in cerebral flow, inflammation and the association with systemic atherosclerosis or the disease of the small vessels of the brain. Although the data are often uncertain and conflicting, it would appear that atrial fibrillation therapy can prevent or slow dementia through three distinct actions: (i) inhibition of left atrial remodelling; (ii) prevention of (micro)-embolism and silent (and not) cerebral infarcts; (iii) increase and regularization of cerebral flow and perfusion. These mechanisms are not mutually exclusive and could be operational in various ways in the individual subject, hence the need to define the pathogenesis of brain damage, so as to customize and optimize the prophylaxis of dementia.

Conflict of interest: None declared.

References

- Gupta A, Giambone AE, Gialdini G, Finn C, Delgado D, Gutierrez J, Wright C, Beiser AS, Seshadri S, Pandya A *et al.* Silent brain infarction and risk of future stroke: a systematic review and meta-analysis. *Stroke* 2016;**47**:719-725.
- Wang Z, van Veluw SJ, Wong A *et al.* Risk factors and cognitive relevance of cortical cerebral microinfarcts in patients with ischemic stroke or transient ischemic attack. *Stroke* 2016;**47**:2450-2455.
- Gardarsdottir M *et al.* Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. *Europace* 2017;**20**:1252-1258.
- Spartera M, Stracquadiano A, Pessoa-Amorim G *et al.* The impact of atrial fibrillation and stroke risk factors on left atrial blood flow characteristics. *Eur Heart J Cardiovasc Imag* 2022;**23**:115-123.
- Bayés de Luna A, Martínez-Sellés M, Bayés-Genís A, Elosua R, Baranchuk A. What every clinician should know about Bayés syndrome. *Rev Esp Cardiol (Engl Ed)* 2020;**73**:758-762.
- Gutierrez A, Norby FL, Maheshwari A *et al.* Association of abnormal P-wave indices with dementia and cognitive decline over 25 years: ARIC-NCS (The Atherosclerosis Risk in Communities Neurocognitive Study). *J Am Heart Assoc* 2019;**8**:e014553.
- Rooney MR, Norby FL, Maheshwari H *et al.* Frequent premature atrial contractions are associated with poorer cognitive function in the atherosclerosis risk in communities (ARIC) study. *Mayo Clin Proc* 2021;**96**:1147-1156.
- Russo C, Jin Z, Liu R *et al.* LA Volumes and reservoir function are associated with subclinical cerebrovascular disease: the CABL (Cardiovascular Abnormalities and Brain Lesions) study. *JACC Cardiovasc Imaging* 2013;**6**:313-323.
- Wang W, Zhang MJ, Inciardi RM *et al.* Association of echocardiographic measures of left atrial function and size with incident dementia. *JAMA* 2022;**327**:1138-1148.
- Jacobs V, Woller SC, Stevens S *et al.* Time outside of therapeutic range in atrial fibrillation patients is associated with long-term risk of dementia. *Heart Rhythm* 2014;**11**:2206-2213.
- Søgaard M, Skjøth F, Jensen M, Kjældgaard JN, Lip GYH, Larsen TB, Nielsen PB. Nonvitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients and risk of dementia: a nationwide propensity-weighted cohort study. *J Am Heart Assoc* 2019;**8**:e011358.
- Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J* 2019;**40**:2327-2335.
- Kühne M, Krisai P, Coslovsky M, Rodondi N, Müller A, Beer JH *et al.* Silent brain infarcts impact on cognitive function in atrial fibrillation. *Eur Heart J* 2022;**43**:2127-2135.
- Lin J, Li CH, Chen YY *et al.* Rhythm control better prevents dementia than rate control strategies in patients with atrial fibrillation—a nationwide cohort study. *J Pers Med* 2022;**12**:572.
- Kim D, Yang P, You SC *et al.* Association of rhythm control with incident dementia among patients with atrial fibrillation: a nationwide population-based cohort study. *Age Ageing* 2022;**51**:1-9.
- Jin MN, Kim TH, Kang KW *et al.* Atrial fibrillation catheter ablation improves 1-year follow-up cognitive function, especially in patients with impaired cognitive function. *Circ Arrhythm Electrophysiol* 2019;**12**:e007197.
- Hsieh YC, Chen YY, Chien KL *et al.* Catheter ablation of atrial fibrillation reduces the risk of dementia and hospitalization during a very long-term follow-up. *Int J Cardiol* 2020;**304**:75-81.
- Bodagh N, Yap R, Kotadia I *et al.* Impact of catheter ablation versus medical therapy on cognitive function in atrial fibrillation: a systematic review. *J Interv Card Electrophysiol* 2022;**65**:271-286.
- Kato N *et al.* Brain magnetic resonance imaging and cognitive alterations after ablation in patients with atrial fibrillation. *Sci Rep* 2021;**11**:18995.
- Mohanty S, Mohanty P, Trivedi C *et al.* Impact of oral anticoagulation therapy versus left atrial appendage occlusion on cognitive function and quality of life in patients with atrial fibrillation. *J Am Heart Assoc* 2021;**10**:e019664.