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Atrial fibrillation: the relation between heart and brain

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Introduction

According to the holistic view in medicine, the entire human organism is primary and the entire organism is greater than the sum of its parts; the parts are related in such a way that their functioning is conditioned by their relationship to each other. Where the atomist believes that any whole can be broken down or analyzed into its separate parts, the holist looks at things or systems in aggregate and argues that we can know more about them in considering them in their interrelationship as part of the whole *(Fig. 1)*.

Non-valvular atrial fibrillation (NVAF) is a typical clinical entity, that can be described in an holistic way, when it manifests itself in elderly patients with atherosclerosis. A description of atrial fibrillation from a holistic view does not mean that the whole spectrum of atrial fibrillation will be discussed. We will not pay attention to the complex electrophysiological substrates in the atrium, which are implicated in the occurrence of atrial fibrillation. Furthermore, we will not refer to valvular atrial fibrillation nor to lone atrial fibrillation in young people. We will neither deal with the influence of the brain on the occurrence of atrial fibrillation, like in the "vagally mediated" atrial fibrillation. Our presentation deals with NVAF in the elderly and will focus especially on the relation of NVAF with manifestations in the brain in these patients.

Non-valvular atrial fibrillation: prevalence and the relation with ischemic stroke

NVAF in the elderly is the most common sustained arrhythmia in clinical practice and its prevalence in people > 65 years reaches 5% and in people > 80 years reaches 10%.[1,2] Because of an ageing population in the Western World the prevalence of NVAF will even rise in the near future and will have increasing clinical and economic importance.[3] NVAF does not only have a strong correlation with increasing age, but the incidence of NVAF is also significantly correlated with diabetes mellitus and metabolic syndrome,[4,5] both of which also show a sharp increase in the last decennia. Therefore, the significance of NVAF as an epidemiological phenomenon should be clear.

The relation of NVAF with ischemic stroke is two-fold. First of all NVAF can be the cause of ischemic stroke as being a source of cardioembolism. It is considered that in people above 65 years one out of each six ischemic strokes is caused by cardioembolism;[5] NVAF is the far most important cause of cardioembolism in these patients. Because of this cardioembolic risk, oral anticoagulation is indicated in most NVAF patients above 65 years[5] and this indication has been confirmed in several large clinical trials *(Fig. 2)*.[6]

NVAF patients in which cardioembolism has been occurred already or in whom stasis in the left atrium is more likely to occur (heart failure, hypertension causing increased end-diastolic left ventricular pressure, etc) are considered to be at highest risk *(Table 1)*.[5]

The second relationship of NVAF with ischemic stroke is given by the fact that both clinical entities in the elderly are often expression of the same underlying atherothrombotic disease. It has been shown that 70% of all NVAF patients above 65 years have carotid artery sclerosis,[7] which is the predominant cause of cerebrovascular events in the elderly. This is the reason, why at least the platelet-inhibitor aspirin should be gi-

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Fig. 1. In the holistic view not the separate parts as such of the organism are investigated, but especially their interrelationship as part of a whole.

ven as prophylactic therapy against ischemic cerebrovascular events in NVAF patients above 60 years without presence of any risk factor.[5] This second non-causal relationship of NVAF with ischemic stroke points at the important issue, that NVAF in the elderly as such is a marker of the presence of atherosclerosis in these patients. NVAF in elderly patients may often be even a marker of advanced atherosclerosis, given the strong correlation of both with factors such as advanced age, inflammation, etc.

Non-valvular atrial fibrillation and inflammation

Until the 1970s the link between lipids and atherosclerosis dominated our thinking. In the past 2 decennia atherosclerosis has more and more been considered as a chronic inflammatory disorder and inflammatory markers have shown to herald myocardial infarction, stroke and peripheral arterial disease.[8-10]

Recently also for NVAF a strong correlation has been found with inflammation, as being expressed by the level of (hs-)CRP and IL-6.[11-13] Patients with higher (hs-)CRP have more recurrences of paroxystic AF and the anti-inflammatory effect of statins reduce the AF recurrences.[12,13] It seems logical that signs of more active inflammation will induce more atherosclerotic alterations in the atrial wall; hence more fibrotic degeneration will occur and this will affect the normal atrial electrical pathways, giving rise to chaotic atrial depolarization waves, so typical for atrial fibrillation. However, another phenomenon that is related with inflammation could also give rise to the appearance of AF. Increased inflammatory activity produces higher levels of acute-phase proteins, of which (hs-)CRP and fibrinogen are well-known exponents. The common effect of all the different acute-phase proteins is, that they increase blood aggregation, leading to higher blood viscosity.[14] In the law of Hagen-Poisseuille (total blood flow $Q= [(\Delta P.\pi.r^4)/8.l] \times 1/\eta$ and blood flow resistance $R = [(8.l)/(\pi.r^4)] \times \eta$ (η = viscosity and r = vessel radius)) higher blood viscosity will increase total blood resistance. No studies so far have been performed to determine the influence of increased blood resistance by higher viscosity on the occurrence of atrial fibrillation. In this aspect should be mentioned, that the presence of left ventricular hypertrophy in hypertensive disease is not correlated so much with the level of arterial hypertension or with the duration of arterial hypertension, but is closely related with the level of blood viscosity in these patients *(Fig. 3)*.[15] Blood viscosity has been found to be an important risk factor for atherosclerosis besides well-known risk factors as hypercholesterolemia, hypertension and smoking.[16,17] A recent clinical study showed that statins reduce the incidence of atrial fibrillation after coronary bypass surgery.[12] This effect of statins cannot be ex-

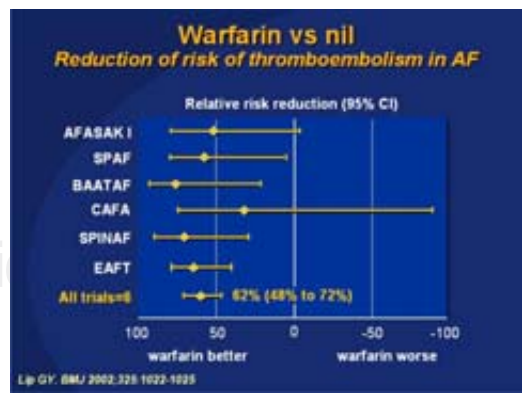

Fig. 2. Several large clinical trials have shown the benefit of oral anticoagulants in the prevention of thrombo-embolic stroke in NVAF patients.

Table I. Classification of risk for cerebrovascular events in NVAF patients and the corresponding recommendations for antithrombotic therapy. (From: Task Force AHA *Circulation* 2006;114).

Risk category	Recommended therapy
— No risk factors	Aspirin 81-325 mg daily
— One moderate risk factor	Aspirin 81-325 mg daily or warfarin
— Any high-risk factor or more than 1 moderate risk factor	Warfarin (INR 2.0-3.0, target 2.5)

Less validated or weaker risk factors	Moderate	High-risk
Female gender	Age greater > 75 years	Previous stroke/TIA
Age 65-74 years	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve
Thyrotoxicosis	LV ejection fraction < 35%	
	Diabetes mellitus	

plained by improved systolic or diastolic performance of the heart or by rapid amelioration of electrical properties of the atrial wall. However, it might be explained by the proven reduction of inflammatory proteins in the blood after statin therapy, which causes lower blood viscosity and alters the hemodynamic conditions for atrial contraction beneficially. Blood flow rate in the atrium is lower and due to the non-Newtonian characteristics of blood, viscosity rises sharply at lower flow rates, increasing the influence of viscosity (η) in the Poisseuille law for atrial performance.[18,19] This concept of inflammation in the blood focuses on inflammation as a whole; inflammation is not only more or less present in the atherosclerotic plaques of the arterial wall.

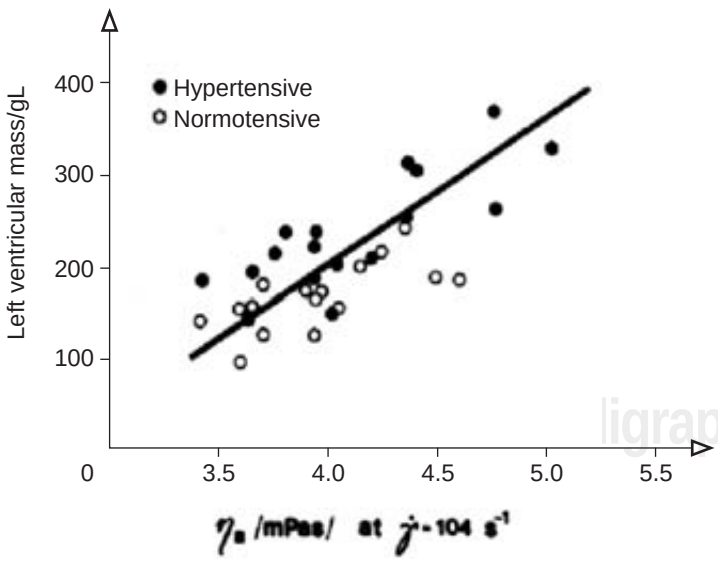

Fig. 3. A strong correlation exists between whole blood viscosity and the occurrence of left ventricular hypertrophy, as detected by echocardiography (From: *Am J Cardiol* 1984;54)

It is concordant with the thinking, that we should focus on the "vulnerable" patient in stead of the "vulnerable" plaque *(Fig. 4)*.[20]

Atrial fibrillation and cognitive impairment

The incidence of cognitive impairment increases sharply with age. Ample evidence is now available that generalized atherosclerotic disease contributes to cognitive decline and dementia. The rate of cognitive decline and the incidence of dementia is higher when systemic atherosclerosis and inflammation are both present. We described previously the high prevalence of atherosclerosis and inflammation in NVAF patients. Therefore, it is understandable why NVAF patients compared to individuals of the same age show more cognitive impairment.[21] This cognitive impairment is also reflected in the presence of more white matter lesions and more silent brain infarcts on the cerebral MRI-images of NVAF patients.[22,23] The strong correlation between NVAF and cognitive impairment becomes even present in the more acute appearance of cognitive decline after cardiac surgery, that is significantly higher in those patients who develop atrial fibrillation post-operatively.[24] Although the pathogenetic link between atrial fibrillation and cognitive impairment is still unclear, the correlation might be explained by the increased blood viscosity. High blood viscosity is detrimental for the atrial hemodynamics as discussed before and also affects significantly the cerebral perfusion. The cerebral perfusion is highly dependent on blood viscosity.[25] Furthermore, atrial fibrillation will diminish cardiac output, which again will reduce flow rate in ce-

Fig. 4. Not only the vulnerable plaque will determine the occurrence of an acute atherothrombotic event, but also the vulnerable blood and (in case of coronary events) the vulnerable myocardium; together they determine the vulnerable patient (From: *Am J Cardiol* 2006;98)

rebrum and hence augment blood viscosity even more.[26]

The finding of increased inflammation with rising blood viscosity in atrial fibrillation suggests that anti-inflammatory agents should be added to the usual therapy of antiplatelets or oral anticoagulants. It has been shown, that the presence of spontaneous echo contrast in the left atrium is correlated with an increased risk of cardioembolic stroke;[27] this spontaneous echo contrast is the reflection of rouleaux formation between the red blood cells, being the expression of higher blood viscosity at low flow rates.[28] Treatment with oral anticoagulants did not reduce the presence of spontaneous echo contrast in the left atrium.[29] Preliminary studies with statins did show a beneficial effect on cognitive function in the elderly, which effect could not be explained by the lipid lowering effect.[30] This pleiotropic effect might even be more beneficial in NVAF patients.

Epilogue

In the previous considerations we have tried to describe NVAF in the elderly not as a simple rhythm disturbance due to a circumscript local atrial electrical defect, but as part of a complex process in which atherosclerosis plays a pivotal role. Therefore, treatment of atrial fibrillation in the elderly should not focus on antiarrhythmic therapy. This has clearly been confirmed by the large AFFIRM and RACE trials, in which rate-control therapy and rhythm control therapy in NVAF patients over 60 years old showed no significant difference in clinical outcome.[31,32] On the other hand, patients with paroxystic NVAF who were treated with AII-antagonists or statins, both of which have shown to have an anti-atherosclerotic effect by reduction of inflammation, showed lower recurrences of atrial fibrillation and better clinical outcome.[33] More clinical studies will appear to demonstrate the beneficial effect of these non-antiarrhythmic agents not only on atrial fibrillation itself, but also on cerebral function, as heart and brain are so closely linked in non-valvular atrial fibrillation in the elderly.

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