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Editorial

Pathophysiological differences between atrial fibrillation subgoups: Is there a fibrillatory-induced atherosclerotic disease progression?

Atrial fibrillation (AF) may cause ischemic stroke, acute myocardial infarction, congestive heart failure, and death [1,2]. Although there are well established risk scores to predict embolic events/stroke and bleding events in AF patients, specific AF subgroups with different risk profiles for negative outcomes have not been well characterized. Despite use of OAC, 35 to 50% of AF patients need hospitalization or die within 5 years [1]. Studies showed that the risk of cardiovascular adverse events is particularly high within the first year after AF diagnosis. The EAST-AFNET4 trial (The Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) which randomly assigned patients who had „early AF" (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either early rhythm control or usual care [2]. The trial had to be stopped early, because the efficacy outcome was reaching. The trial clearly showed that early rhythm-control strategy was associated with a lower risk of cardiovascular outcomes than usual care among early AF patients.

The study by Watanabe et al. [3] included a total of 7406 patients in the prospective Japanese J-Rhythm registry at 158 study sites. The aim of the study was to identify the clinical phenotypes of AF. Data of an observational cohort that included 7406 patients with non-valvular AF Endpoints were defined as all-cause mortality, thromboembolism, and major bleeding. The authors found 4 different phenotypes of AF patients based on 40 characteristics: [1] a younger age and low rate of comorbidities [2], a high rate of hypertension [3], high bleeding risk [4], prior coronary artery disease and other atherosclerotic comorbidities. Of note, the atherosclerotic phenotypes had highest adjusted risks of total mortality and major bleeding.

The current study adds important information about outcome in different AF subgroups. In particular, AF patients with atherosclerotic comorbidities appear to have worse prognosis. It is of upmost importance to realize that AF patients are not equal with regard to prognosis and that the preexsisiting clinical conditions have major impact on outcome. So far, prevention of stroke and embolic events were extensively studied and new OAC have been successfully introduced in AF therapy. However, the true impact of the clinical AF phenotypes is less well studied. In this context, main questions are: what ist he impact of AF pattern on outcome? are there outcome differences between clinical AF subgroups?. Pathophysiologically, AF is known to affect microvascular flow in different organs [1,4,5]. In particular, the left ventricle, specific areas in the brain and the kidneys appear to be affected by these microvascular flow abnormalities. Bukowska et al. analyzed in a pacing model the impact of AF on molecular and structural renal changes [4]. It was shown that renal expression of endopetidases was down-regulated by rapid atrial pacing, whereas fibrotic TGF-beta1 was up-regulated. Neurohumoral factors like aldosterone, atrial natriuretic peptides, asymmetric dimethylarginine, and angiotensin peptides did not induce the observed down-regulation of peptidase expression in renal cellular models [4]. Thus, the irregular rhythm rather than indirect humoral factors induced functional and structural kidney changes. In the clinical setting, the majority of AF patients has comorbidities, which indeed may further alter vascular biology, and thereby, organ function [5–10]. The results by Watanabe et al. show that in this context the presence of vascular sclerosis might be useful to identify a specific subgroups of AF patients, who are at high risk for adverse outcome [3]. The AF-induced oxidative stress, which is also present within the vascular endothelium, might be one explanation for the present findings [6–10]. Thus, limitation of blood flow and oxygen supply in combination with increase cellular oxidative stress might interact to cause acute events and/or disease progression. Studies could show that paroxysmal AF is associated with high rates of ACS [11,12]. A fascinating aspect would be to identify AF as a risk factor for atherosclerosis progression. At present, there is indirect evidence (loss of vascular nitric oxide, activation of oxidative stress pathways, increased adhesion molecules and macrophage recruitment factors etc) to show vascular alterations during AF. Pathophysiologically, factors listed in the CHA2DS2-VASc score contribute to a thrombogenic endocardial remodeling process, which predominantly occurs in the left atrial appendage [2]. In addition, CHA2DS2-VASc Score parameters predict the occurrence of ACS and mortality. Thus, the CHA2DS2-VASc Score per se might be considered to be a vascular risk score [2]. Nevertheles, a score value does not identify all clinical entites (see Fig. 1).

Nevertheless, the present study from the J-Rhythm registry has limitations: only Japanese patients were studied. Thus, it is not fully clear if regional differences with regard to atherosclerosis and other co-factors exists in other parts of the world as well. Registries are not fully controlled, and therefore, there is potential recruitment bias. In addition, subgroups within the J-Rhythm registry were not balanced. These factors must be considered if the results were extrapolated to all AF patients.

Nevertheless, the study by Watanabe et al. adds an important piece to the puzzle of AF. The authors need to be congratulated. The results may open a new field of research aiming to assess the presence of clinically relevant AF subgroups. At present, "fibrillatory atherosclerotic disease progression" is a provocative theory.

Declaration of Competing Interest

The authors declare that they have no known competing financial

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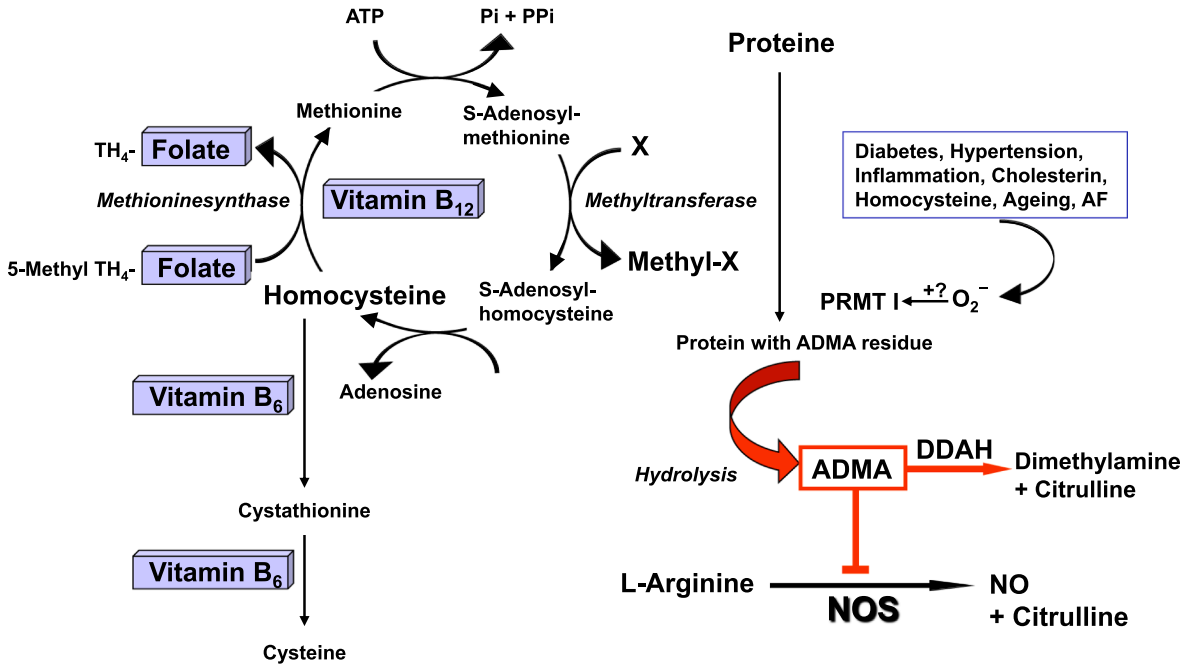

Fig. 1. Impact of atrial fibrillation (AF) and Co-factors on nitric oxide (NO) metabolism and interaction with endothelial NO Synthase (eNOS) including asymmetric dimethylarginine (ADMA). For details see text.

interests or personal relationships that could have appeared to influence the work reported in this paper.

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