Arterial Stiffness Predicts Incident Atrial Fibrillation in the Framingham Heart Study

A Mechanistic Contribution in People With High Blood Pressure or History of Hypertension

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See related article, pp 590–596

Hypertension is, due to the high prevalence in the general population, by far the most important risk factor for the development of atrial fibrillation (AF). A recent study confirmed that blood pressures even in the upper normal or prehypertensive range are associated with an increased risk of AF.[1] Independently, in people with high cardiovascular risk,[2] left ventricular hypertrophy, serum creatinine, history of hypertension, and history of cerebrovascular disease were highly significant predictors, as were body mass index and history of coronary heart disease. This analysis[2] of populations participating in 2 large outcome trials of similar design (n=30 424) documented the connection between hypertension, or its end-organ damage as well as risk factors, and the risk of incident AF. The relationship between the history of hypertension and risk of AF persists, despite confounding by the extensive vascular disease or complicated diabetes mellitus that the participants had,[2] or maybe these diseases even escalated the relationship.

The dominating role of high blood pressure in the pathogenesis, pathophysiology, prediction, diagnosis, and treatment of AF has been extensively reviewed by a working group of the European Society of Hypertension.[3] Perhaps the most remarkable finding was that up to ≈90% of patients with AF who participated in some of the recent large randomized clinical outcome trials of new anticoagulant or antiarrhythmic medications in people with AF had a history of hypertension[3] even without baseline workup using ambulatory 24-hour blood pressure measurements to detect people with masked hypertension. This suggests that AF is in most cases a typical complication of hypertension, and even more so than stroke or heart failure.

It is not entirely surprising but confirmatory in a slightly different type of population that left ventricular hypertrophy is a strong predictor of AF. In a large study of patients with left ventricular hypertrophy (n=9193), blood pressures, Cornell voltage-duration product left ventricular hypertrophy on ECG, heart rate, age, and male sex were the predictors.[4] In this study, there was less incident AF with regression of left ventricular hypertrophy during antihypertensive treatment.[5] Because a difference in stroke drove the difference in the primary end point in favor of angiotensin receptor blocker over β-blocker,[4,5] it is not particularly surprising that less new-onset AF during treatment with angiotensin receptor blocker compared with β-blocker contributed to fewer incident strokes and the difference in the primary composite end point. Furthermore, hypertension is a strong factor in not only remodeling left ventricular structure but also strongly related to left atrial size.[6] Increased left atrial size then implies stretching of the atrial myocardial fibers, which again leads to less cross-talk between atrial myocardial cells provoking AF. In addition, data from the same study suggested that reducing left atrial size during antihypertensive therapy translates into reduced risk of new-onset AF.[7] A recent and detailed analysis[8] shows that, in patients with left ventricular hypertrophy, pulse pressure was equivalent to systolic and diastolic blood pressures combined in predicting new-onset AF, but when forced into the same statistical model, the pulse pressure was by far the strongest predictor of new-onset AF among the various blood pressure components. This strong association with pulse pressure suggests that in advanced hypertensive disease, the stiff arteries with high hemodynamically increased afterload and stretch of atrial walls with atrial chamber dilation and pressure up into the pulmonary veins may be a key mechanism for promoting unstable electric properties that lead to AF. The presence of left ventricular hypertrophy by ECG, increased age, and coronary heart disease were similarly significant confounding covariates in another large population (n=15 245) of hypertensive people participating in a clinical trial also with proper serial ECG detection of incident AF.[9] New-onset AF strongly portended an increased risk of congestive heart failure,[9] which may be explained by the fact that people with the more advanced cardiac disease cannot sustain the impact of losing approximately 20% to 25% of their cardiac output by losing the atrial component of left ventricular filling. However, maybe more important, the unfavorable hemodynamic state of increased vascular stiffness and hypertension may lead to increased left ventricular filling pressures, increased left atrial volumes, and increased left atrial pressure that per se leads

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(*Hypertension*. 2016;68:555-557.
DOI: 10.1161/HYPERTENSIONAHA.116.07671.)

Hypertension **is available at http://hyper.ahajournals.org**
DOI: 10.1161/HYPERTENSIONAHA.116.07671

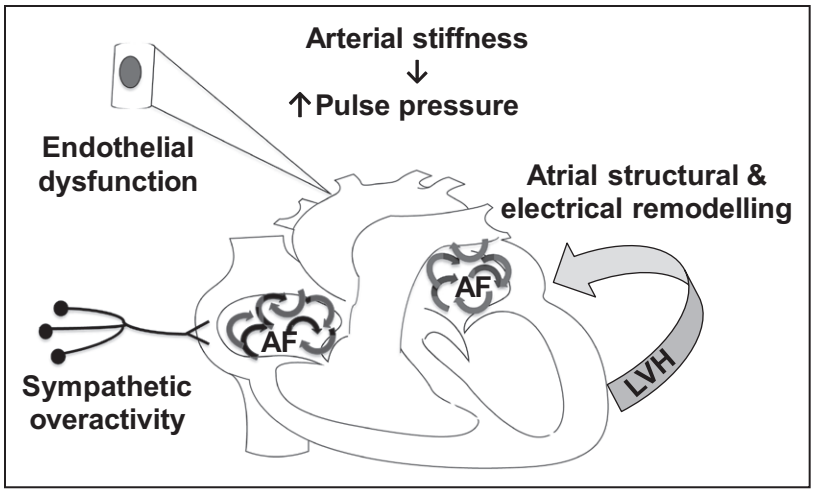

Figure. Possible mechanisms for the linkage between hypertension and atrial fibrillation (AF). Endothelial dysfunction is a general vascular effect, however, simplified as an endothelial cell in the artery (aorta) in the figure. Arterial stiffness increases pulse pressure and then the cardiac afterload, which may induce both left ventricular and atrial structural and electric changes that may promote AF as further explained in the text. Sympathetic overactivity may precede hypertension and promote AF. LVH indicates left ventricular hypertrophy.

to increased risk of congestive heart failure, where AF is the clinical phenotype of this condition. In addition, incident AF was strongly associated with heart failure in these high-risk hypertensive people[9] whether they had diabetes mellitus, incident diabetes mellitus, or no diabetes mellitus, although the patients with both hypertension and diabetes mellitus had twice the risk of getting heart failure compared with the hypertensive patients without diabetes mellitus.

The relationship between arterial stiffness, pulsatile hemodynamic load, and endothelial dysfunction to incident AF have not been fully understood as pointed out by Shaikh et al[10] in an article reported in this issue of *Hypertension*. To better understand the pathophysiology of AF, they examined associations between noninvasive measures of vascular function and new-onset AF.[10] The study sample included participants with the age of ≥45 years without AF at the outset from the Framingham Heart Study Offspring and Third Generation Cohorts. Using Cox proportional hazards regression models, they examined the relationship between new-onset AF and tonometry measures of arterial stiffness (carotid-femoral pulse wave velocity), wave reflection (augmentation index), pressure pulsatility (central pulse pressure), endothelial function (flow-mediated dilation), resting brachial arterial diameter, and hyperemic flow. AF developed in 407 of 5797 participants examined in the tonometry sample and in 270 of 3921 participants studied in the endothelial function sample during a median of 7.1 years of follow up. Higher augmentation index (P=0.02), central pulse pressure (P=0.04), baseline brachial artery diameter (P=0.04), and lower flow-mediated dilation (P=0.02) were associated with increased risk of incident AF. Higher pulsatile load assessed by central pulse pressure and greater apparent wave reflection measured by augmentation index were associated with increased risk of new-onset AF. Vascular endothelial dysfunction assessed by lower flow-mediated dilation, and higher baseline brachial arterial diameter may precede development of AF. These measures may be additional risk factors or markers of subclinical cardiovascular disease associated with increased risk of incident AF.

Participants were diagnosed with AF if AF or atrial flutter was present on an ECG obtained from outside hospital or physician records or from routine Framingham clinic examination with ECG (every 4–8 years in the offspring and third-generation cohorts).[10] The relationships were significant even when adjusted for clinical parameters, age and other risk factors, including hypertension. However, it should be pointed out that increments in the variables of arterial stiffness and function that were examined are typical for people with high blood pressure or history of hypertension and that the authors did not specifically address whether the association of these measures of arterial stiffness, pulsatile hemodynamics, and endothelial dysfunction with new AF were independent of the previously demonstrated predictive value of brachial blood pressure measurements in this population. In the Framingham Heart Study,[10] like in other studies,[8] peripheral pulse pressure was the dominating blood pressure component for predicting incident AF.

The strength of the study by Shaikh et al[10] is the large, prospective, community-based cohort design and long follow-up, as well as rigorous adjudication of all potential cases of new-onset AF. There were also several limitations of the study as pointed out by the authors.[10] The observational nature precludes any causal inference and the authors cannot of course exclude residual confounding by duration or severity of associated risk factors or unmeasured common risk factors. They evaluated a middle-aged and older cohort of white study participants, and their results may, thus, not be generalizable to younger individuals or those from nonwhite racial groups. They did not analyze subtypes of AF mainly paroxysmal and persistent separately, and they cannot exclude the possibility that some clinically unrecognized cases of AF might have been missed. The latter may be the most interesting; systematic taking of ECG has been introduced into at least some large outcome trials,[2,4–9] which has contributed to clarify effects of specific treatments for lowering of blood pressure, such as inhibiting the renin–angiotensin system and observing benefits of normalization of left ventricular hypertrophy and increased left atrial size.[5,7] However, taking annual ECGs may still miss several patients with incident paroxysmal AF and new and feasible methods for more or less continuous monitoring in mega-trials are needed.

Taken together with previous literature, these new data from the Framingham Heart Study[10] contribute to an evolving mechanistic framework for how people with high blood pressure or hypertension history develop an increased risk for

developing AF (Figure). Whether high blood pressure is the cause of the arterial stiffening, structural vascular changes, left ventricular hypertrophy, and increase atrial size, or merely a marker of the same vascular disease, is unclear, but high blood pressure can be much more easily detected and usually by itself provide the rationale for adequate treatment. Understanding the mechanisms in play may, however, focus on earlier detection and prevention of AF in people with hypertension, hopefully avoiding the multiplying effect of AF on the risk of stroke, heart failure, and sudden cardiac death in this setting.[4–9]

Disclosures

S.E. Kjeldsen has received honoraria for lecturing and consultancy from Bayer, Merck & Co, and Takeda. The other authors report no conflicts.

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Hypertension
Journal of the American Heart Association

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Hypertension. 2016;68:555-557; originally published online July 25, 2016;
doi: 10.1161/HYPERTENSIONAHA.116.07671
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563