AF results from the occurrence of 3 mechanisms (3,4): 1) single-circuit re-entry; 2) multiple circuit re-entry; or 3) rapid focal ectopic activity. Maintenance of AF requires that an appropriate substrate exist on which a trigger can initiate re-entry. The substrate for AF consists of 2 components: 1) altered electro-physiological properties; and 2) altered structural properties of the atrium. Uncontrolled hypertension can result in several changes to the left atrial substrate including effects on ion channel function and increased atrial fibrosis (Figure 1) (5–7).

Despite advancements in ablation technologies over the past decade, including contact force technology and the second-generation cryoballoon, the recurrence rate of AF after catheter ablation remains high (8–10). These observations have led those of us who treat AF to examine other contributors to AF, with the realization that ablation alone may be insufficient to result in optimal arrhythmia control in patients. Hypertension is an obvious target given that is the most prevalent and potentially modifiable risk factor for AF (11,12). Multiple animal and clinical human studies have found a direct relationship between the risk of AF and systolic and diastolic blood pressure (13–20).

In this issue of JACC: Clinical Electrophysiology, Santoro et al. (21) report results of a carefully conducted prospective cohort study of 531 consecutive patients who underwent ablation for AF grouped by uncontrolled hypertension (n = 160), controlled hypertension (n = 192), or no hypertension (n = 179). All patients underwent pulmonary vein (PV) antral isolation with additional ablation performed for non-PV triggers, as determined by operator discretion. The main findings of this study were that uncontrolled hypertension, as measured before the procedure, was associated with a significantly increased risk of recurrence (40.6%) at a follow-up of 19 ± 7.7 months after a single ablation procedure compared with those patients who had controlled hypertension (28.1%) or no hypertension (25.7%). The presence of non-PV triggers was greater (58.8% vs. 33.3%) in the group with uncontrolled hypertension. Ablation of non-PV triggers was associated with a significant reduction in AF recurrence compared with those whose non-PV triggers were left alone (69.8% vs. 37.3%).

This study is certainly compelling in advancing the notion that blood pressure control is indeed exquisitely linked to recurrence of AF after catheter ablation. There are, however, important caveats to this study that prevent this trial from being definitive. The lack of randomization is an obvious limitation of this study, recognized by the authors. Most importantly, this study did not address the effect of aggressive blood pressure control and its interaction with outcomes of catheter ablation. This is a key question that needs to be addressed in order to assess how hypertension may affect the genesis of AF. Differences in left atrial size and the presence of a left atrial scar are also important confounders that are known to have an effect on ablation outcome (22,23). Important measurable and unmeasurable confounders not accounted for in this study include the duration of AF, presence of sleep apnea (23,24),...
and variations in the autonomic nervous system, which may introduce bias (25). The importance of central sympathetic inhibition in hypertensive patients was demonstrated by Giannopoulos et al. (26), where the use of moxonidine, a centrally acting sympathoinhibitory agent, reduced the recurrence of AF post-ablation at 12 months, without any major effect on blood pressure. The reduction in AF observed by Pokushalov et al. (27), in a study of renal denervation as an adjunct to AF ablation, may have been due to modulation of sympathetic outflow rather than blood pressure reduction. Finally, the ablation procedure itself differed among and within groups; the determinants of when ablation for non-PV triggers was performed are not reported.

Risk factor management for patients with AF before catheter ablation is an emerging area of study (24). A multicenter clinical trial (NCT00438113) (SMAC AF [Atrial Substrate Modification With Aggressive Blood Pressure Lowering to Prevent AF]) is almost complete in Canada to demonstrate whether substrate modification with aggressive blood pressure lowering, with antihypertensive therapy, as an adjunct to AF ablation has a beneficial effect for reducing AF recurrence. Other studies examining novel drug approaches to sympathetic modulation, ganglionated plexus ablation, and other therapies may also add to our increasing understanding of the genesis of AF (28).

This study by Santoro et al. (21) confirms that AF is not simply a rhythm disorder that can be tackled by catheter ablation or through variation of that approach, but rather by increasing our understanding of the determinants of progression of atrial substrate that give rise to maintenance of AF. Elimination of triggers is only part of the equation, and if we fail to address those factors that maintain and promote substrate, the struggle to effectively treat AF will continue.

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FIGURE 1 Mechanism of Blood Pressure Effect on Substrate for AF

![Image](https://via.placeholder.com/150)

Modified and reproduced with permission from Ehrlich et al. (7). BP = blood pressure; LV = left ventricular.

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