Hypertension Research
https://doi.org/10.1038/s41440-024-01694-8

COMMENT

# Exploring the relationship between nocturnal hypertension and atrial fibrillation recurrence

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**Keywords** Blood pressure · Non-dipping · Hypertension-mediated organ damage · Left atrium enlargement · Atrial fibrillation

Received: 23 March 2024 / Accepted: 2 April 2024


According to the latest European Society of Hypertension (ESH) guidelines [1], nocturnal hypertension is defined as a mean blood pressure (BP) ≥ 120/70 mmHg recorded by Ambulatory blood pressure monitoring (ABPM) during the nocturnal hours. To establish the circadian rhythm of BP and the nocturnal BP profile (defined as the presence/absence of the nocturnal physiological BP fall or "dip" of BP) may provide significant additional prognostic information in hypertensive patients: nocturnal BP is recognized as a cardiovascular risk compared to the physiological BP dipping pattern, independent of absolute BP load, and is more predictive of adverse outcomes, including cardiovascular (CV) events and mortality, than 24-h or daytime BP [2, 3]. This additional information provided by ABPM has been driving the debate for years to expand the established indications for the use and periodic reassessment of ABPM [1–3].

The heart is one of the main targets of hypertension-mediated organ damage (HMOD) [1], leading to several structural and functional alterations, the most relevant of which are left ventricular (LV) geometric changes, left ventricular hypertrophy (LVH), impaired diastolic and systolic ventricular function and left atrium (LA) enlargement. The use of two-dimensional transthoracic echocardiography (2D-TE), which is indicated in all hypertensive patients [1], allows the collection of data also in a preclinical phase and in asymptomatic subjects in order to prevent, delay, and better manage the most common cardiac diseases directly attributable to chronic elevated BP: heart failure (HF), coronary artery disease (CAD), sudden death and, finally, atrial fibrillation (AF). Patients with nocturnal hypertension are reported to be more likely to develop cardiac damage than those with preserved dipping phenomenon [4], but no data on the occurrence or recurrence of AF have been reported to date.

Pulmonary vein isolation (PVI) ablation is a minimally invasive, widely used procedure for the treatment of AF in patients who are clinically refractory to or contraindicated for antiarrhythmic drugs. Since hypertension-induced LA structural remodeling is a major pathophysiologic factor for the development of AF and there is a considerable lack of evidence for an association with nocturnal hypertension, Watanabe et al. demonstrated in 76 patients undergoing their first PVI ablation procedure that a non-dipper nocturnal BP profile was associated with a 2.8-fold higher risk of AF recurrence than dippers (hazard ratio: 2.78; 95% CI: 1.05–7.34; $p$: 0.039), independent of 24-h BP during a median follow-up of 1138 days after PVI [5].

Of note, in this study, no subject in the non-dipper group had HF, the mean estimated glomerular filtration rate (eGFR) was rather good (65.7 ± 15.5 ml/min/1.73 $m^2$), and the mean nocturnal SBP was 127 ± 16 mmHg, suggesting an even higher risk of AF recurrence in subjects with greater predisposing factors for cardiac damage with greater LA involvement and/or higher nocturnal SBP values.

Diastolic dysfunction may lead to a reduction in LA passive emptying, thereby increasing LA pressures during atrial diastole and eventually causing LA enlargement. Persistence of this pathological stimulus over time may also induce electrical remodeling, leading to greater dispersion of atrial repolarization and, hence, susceptibility to AF. LA dilation would also induce electrical decoupling between muscle bundles, further facilitating the initiation and maintenance of multiple small re-entrant wavelets to sustain

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Published online: 08 May 2024

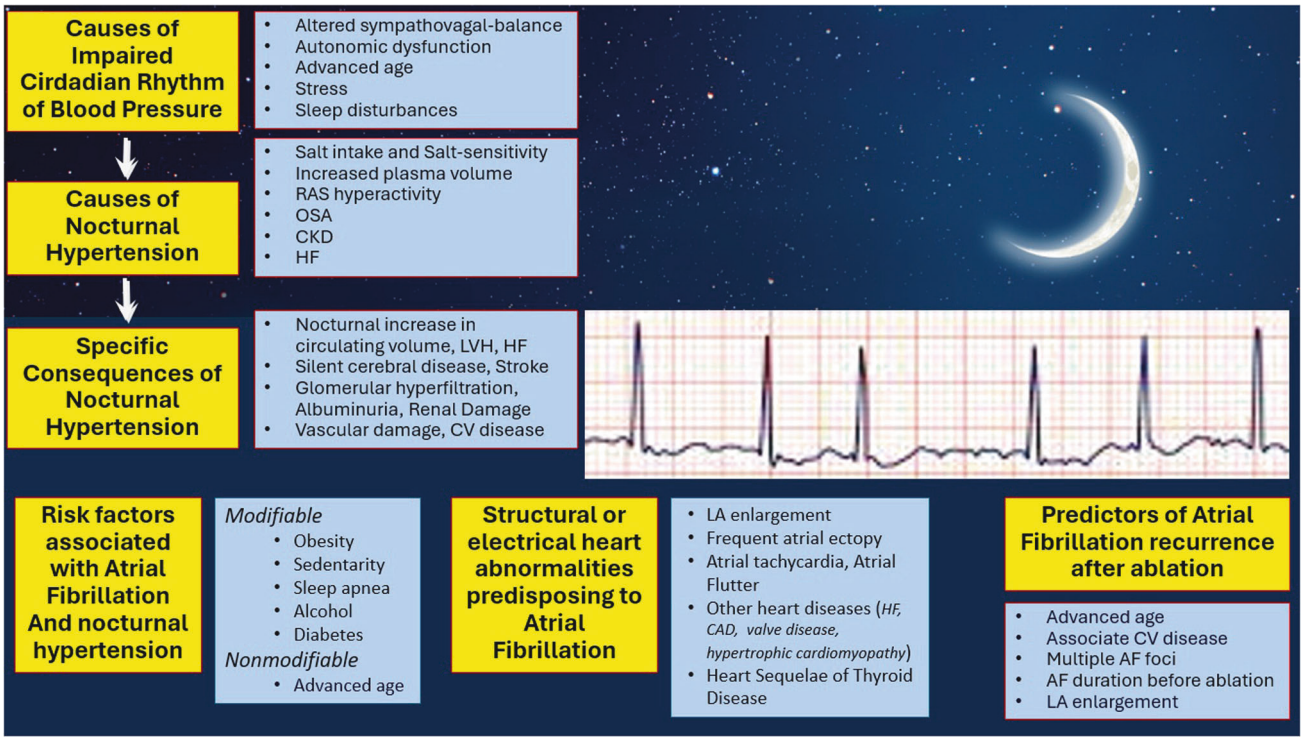


**Fig. 1** Risk factors, mechanisms and pathways linking atrial fibrillation and nocturnal hypertension. OSA indicates obstructive sleep apnea, CKD chronic kidney disease, RAS renin-angiotensin system, HF heart failure, CAD coronary artery disease, CV cardiovascular, LA left atrium, LVH left ventricular hypertrophy. The picture shows the various possible epidemiological, clinical, and electrophysiological links between nocturnal hypertension and the development and recurrence of atrial fibrillation, even after PVI ablation

this arrhythmia [6]. Nevertheless, AF events in hypertension reflect not only structural changes but also an inflammatory background with a somewhat relevant and independent pathogenetic role [7].

In a large cohort ($n = 2482$) of untreated hypertensive subjects in sinus rhythm and free of overt cardiovascular disease or hyperthyroidism, age and LV mass were found to be the only independent predictors of AF, whether LA atrial size was an independent predictor of chronicity of AF [8]. These same factors, in addition to an unfavorable comorbidity burden and relatively uncontrolled hypertension, have been associated with a higher risk of AF recurrence [1, 6–8].

The findings of Watanabe et al. [6] that the non-dipper phenomenon was associated with a higher risk of AF relapse after PVI ablation cannot be easily explained. Several mechanisms can lead to nocturnal hypertension, including increased sympathetic nervous system (SNS) activity, autonomic dysfunction, impaired baroreflex sensitivity, salt sensitivity, increased plasma volume, RAS hyperactivity, OSA and other sleep disturbances, increased stress and renal dysfunction [1] (see Fig. 1). Some of this can be pointed out, such as SNS overactivity. This may be a feature of a significant proportion of patients with high BP and blunted nocturnal falls, although determining the exact proportion of hypertensive patients with sympathetic overdrive appears to be difficult, not only because of the multiple interferences and the constant interplay between the various determinants of sympathetic tone (and sympatho-vagal balance) but also because of the considerable uncertainty regarding the validity of the methods used to assess sympathetic tone [9].

An interesting and closely related issue may be how an appropriate chronotherapy for hypertension might affect arrhythmic events. Recently, a prospective RCT found that randomization to evening or morning drug administration did not result in a difference in CV outcomes, although there was a greater nocturnal BP reduction with bedtime administration [10]. Again, the occurrence of AF was not an outcome of this RCT, and given the randomized design, a clinical decision of evening or bedtime drug administration in established nocturnal hypertension may result in greater benefit for this specific group of subjects; the question remains open.

In conclusion, this paper highlights non-dipping as a possible trigger for AF recurrence even in subjects without a major determinant of nocturnal hypertension, such as obstructive sleep apnea syndrome, opening a new interesting line of research and adding further prognostic relevance to the altered circadian rhythm of BP. Several questions remain unanswered, such as the extent of LA remodeling in non-dippers, the importance of long-term stability of the non-dipper profile, taking into account the influence of therapy or other confounding factors that may further influence nocturnal BP

levels, the role carried out by gender, the relevance of sympathetic nervous system overactivation.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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