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# INNOVATION AND DEVELOPMENT IN WORLD SCIENCE

## PROCEEDINGS OF IV INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE FEBRUARY 2-4, 2026

## ZURICH 2026

# THE LINK BETWEEN RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM ACTIVATION AND ENDOTHELIAL DYSFUNCTION MARKERS AMONG PATIENTS WITH HYPERTENSION COMBINED WITH PAROXYSMAL ATRIAL FIBRILLATION

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**Introduction.** Hypertension (HT**)** and paroxysmal atrial fibrillation (AF) are prevalent cardiovascular diseases, with their incidence steadily rising with age. The frequent co-occurrence of HT and paroxysmal AF suggests shared pathophysiological mechanisms and interconnected risk factors. Hypertension is the most significant modifiable risk factor for the development of atrial fibrillation. Elevated blood pressure promotes structural and electrical remodeling of the heart, including atrial enlargement, fibrosis, and pressure overload [1, 2].

Elevated blood pressure in hypertensive patients is commonly associated with endothelial dysfunction**.** This imbalance between vasodilating and vasoconstricting systems exacerbates the progression of arterial hypertension. Furthermore, heightened activity of free radical oxidation processes contributes significantly to HT progression.

An excessive concentration of peroxides, for instance, accelerates the breakdown of nitric oxide (NO), thereby diminishing its bioavailability and ultimately impairing the vasodilatory capacity of the vascular endothelium. Modern pathophysiological theories recognize the vascular endothelium as an active, dynamic structure critically involved in the synthesis of vasoactive substances and the regulation of disaggregant and fibrinolytic processes [3, 4].

Angiotensin II (Ang II), a stable and biologically active octapeptide, exerts a potent vasoconstrictor effect. Renin-angiotensin-aldosterone system (RAAS) activation, and consequently renin secretion, is tightly regulated by several key mechanisms: arterial pressure within the renal arteries, sympathetic nervous system activity, sodium balance, and a negative feedback loop involving Ang II itself, which manifests as reduced nitric oxide (NO) production. The pro-fibrillatory effects of aldosterone are well-documented, primarily associated with its role in promoting atrial cardiomyocyte fibrosis, hypertrophy, inflammation, and extracellular matrix remodeling.

Crucially, the connection between aldosterone and AF extends to aldosterone-induced electrophysiological alterations in cardiomyocytes that can sustain and perpetuate the arrhythmia. Substantial evidence strongly implicates RAAS in the pathogenesis of AF. This body of research suggests that RAAS plays a more pivotal role in the initiation and progression of AF than merely acting as a factor of comorbid pathology. This compelling evidence underscores the rationale for investigating the intricate interrelationships between RAAS indicators and markers of endothelial dysfunction [5, 6, 7].

**The aim of the work** – to determine the the link between renin-angiotensin-aldosterone system activation and endothelial dysfunction markers among patients with hypertension combined with paroxysmal atrial fibrillation.

**Materials and Methods.** A prospective, open comparative study was conducted at the MNE"City Hospital No. 10" of the Zaporizhzhia City Council. Patient sampling took place from 2018 to November 2019. The study results are based on comprehensive examination and dynamic observation of 136 patients with hypertensive disease, including 100 patients with HT combined with paroxysmal AF and 36 patients with HT without AF. 33 practically healthy volunteers were examined on an outpatient basis at the MI "Regional Medical and Physical Culture Dispensary" of the Zaporizhzhia Regional Council. Patients signed an "Informed Consent Form for Participation in the Study".

*Inclusion criteria included*: male and female patients aged 46 to 65 years;

recurrent paroxysmal atrial fibrillation; verified stage II hypertensive disease; known disease duration >1 year and patient consent for observation.

*Exclusion criteria included:* atrioventricular block II-III degree; ventricular arrhythmias; circulatory failure greater than NYHA class II; oncological diseases; thyroid dysfunction; diabetes mellitus; hemodynamically significant heart defects; drug addiction; alcohol dependence; presence of mental disorders and patient refusal of observation during the follow-up period.

All patients underwent physical examination and standard clinical laboratory and instrumental diagnostics: complete blood count, urinalysis, 12-lead ECG. Biochemical blood tests included glucose, total protein, creatinine, total bilirubin, alanine and aspartate transaminases, and lipid levels. AF presence was determined by ECG changes during examination. Patients were divided into groups based on inclusion/exclusion criteria and the presence of comorbid AF:

*Group 1* included 100 patients with HD combined with AF (median age 60.00 [54.00; 63.00] years);

*Group 2* included 36 patients with HD without AF (median age 57.00 [54.00; 61.00] years);

*Group 3* comprised 33 practically healthy volunteers (median age 56.00 [55.00; 59.00] years).

All 169 examined individuals were comparable in terms of age, social status, and sex.

Plasma levels of angiotensin-II and aldosterone were determined using the enzyme-linked immunosorbent assay (ELISA) method with the commercial Human Ang-II (Angiotensin II) ELISA Kit (Elabscience, USA) and the ALDOSTERONE ELISA kit (Diagnostics Biochem Canada Inc., Canada), according to the manufacturers' instructions. Plasma concentrations of angiotensin-II and aldosterone were expressed in pg/mL.

Stable end metabolites of nitric oxide in blood were determined using a method based on the reduction of nitrate to nitrite, followed by the determination of nitrite using the Griess reaction. Nitrite concentrations were calculated using a calibration

curve constructed with sodium nitrite standards. The study yielded three results: nitrite ion ($NO_2$) concentration (μmol/l), nitrate ion ($NO_3$) concentration (μmol/l), and the total concentration of nitrite and nitrate ions ($NO_2 + NO_3$) (μmol/l).

Statistical analysis of the obtained data was performed using a personal computer with the PSPP software package (version 1.2.0, GNU Project, 1998-2018, GNU GPL license). The distribution of each studied parameter was analyzed, and the data were presented as median (Me) and interquartile range (Q25;Q75). The relationship between variables was assessed using correlation analysis; depending on the data distribution, Pearson's (r) or Spearman's (R) correlation coefficient was evaluated.

**Results and Discussion.** The aldosterone level in patients with hypertension combined with atrial fibrillation was 172.42 (142.06; 193.15) pg/mL and was comparable with 171.41 (129.53; 194.35) pg/mL in the group HT without AF ($p>0.05$) and significantly highe healthy individuals, where it was 124.95 (115.99; 134.23) pg/mL ($p<0.05$). No significant differences were found in such a RAAS parameter as angiotensin II between the groups HT, whereas, in comparison with the healthy control group, where this indicator was 312.58 (274.65; 335.46) pg/mL, it was significantly higher in the group HT combined with AF by 1.7 times, and in the group HT without AF by 1.58 times ($p<0.05$).

The $NO_2$ level was lowest in the group of patients with hypertension combined with AF, at 6.14 (5.62; 6.66) μmol/L, and was significantly lower by 9.31% compared to the group HT without AF – 6.77 (6.34; 7.12) μmol/L, as well as by 22.47 % compared to the value of 7.92 (7.25; 8.26) μmol/L in practically healthy individuals ($p<0.05$). The $NO_2$ level was also 14.52% lower in the group HT without AF, 6.77 (6.34; 7.12) μmol/L, compared to 7.92 (7.25; 8.26) μmol/L in practically healthy individuals ($p<0.05$). The $NO_3$ level in practically healthy individuals was 14.24 (13.08; 15.04) μmol/L, which was highly significantly higher by 22.05% and 20.65% compared to the group HT combined with AF and the group HT without AF, respectively ($p<0.05$).

The comparative evaluation of aldosterone and angiotensin II levels and nitric

oxide metabolites in blood plasma using correlation analysis among patients with HT combined with AF revealed significant moderate correlations between the levels of: aldosterone and $NO_2$ in blood plasma (R = -0.26, p=0.01); aldosterone and $NO_3$ in blood plasma (R = -0.23, p=0.02); aldosterone and $NO_2$+$NO_3$ (R = -0.24, p=0.01); and angiotensin II and $NO_3$ in patients with HT combined with AF (R = -0.21, p=0.04).

Our findings align with existing research, confirming the frequent co-occurrence of hypertension and atrial fibrillation**.** Both conditions are independently linked to endothelial dysfunction, with hypertension further exacerbating this dysfunction in patients already experiencing AF. Specifically, angiotensin II stimulates endothelin-1 production, which further promotes vasoconstriction and exacerbates endothelial impairment. In patients presenting with both HT and paroxysmal AF, the RAAS appears to be a central pathological link. It not only contributes to elevated blood pressure but also intensifies endothelial dysfunction, potentially establishing a vicious cycle that encourages arrhythmia recurrence.

While the role of endothelial dysfunction in AF was historically thought to be an indirect effect primarily impacting atrial thromboembolism, growing evidence now supports its direct contribution to the development and maintenance of atrial arrhythmogenesis, ultimately provoking adverse events associated with AF. This assertion is further supported by studies, such as that by T. Komatsu et al., which confirm the association between endothelial dysfunction and the progression and frequency of AF recurrence [8, 9].

Thus, considering the distinct yet interconnected roles of RAAS and endothelial dysfunction in HT and AF, investigating their intricate interaction in patients with both conditions is crucial for a comprehensive understanding of the underlying pathophysiology. Unraveling this relationship could reveal promising therapeutic targets for managing these complex patients.

**Conclusions**

1. Comparable increases in RAAS indicators were found in patients with

HT combined with AF and those without AF.

2. The $NO_2$ level was significantly lower in the group of patients with HT combined with AF compared to the group without arrhythmia.

3. A significant inverse relationship was found between RAAS indicators and nitric oxide metabolites in patients with HT combined with AF.

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