News on angiotensin II and atrial fibrillation: from the molecular to the pathophysiological

Novedades sobre angiotensina II y fibrilación auricular: de lo molecular a lo fisiopatológico

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ABSTRACT

Introduction: atrial fibrillation is the most prevalent arrhythmia in the world, having high morbidity and mortality rates. Numerous studies have shown the involvement of the angiotensin renin system in the pathogenesis of atrial fibrillation, and in several of these, the underlying mechanism involving a process of atrial tissue remodeling is speculated.

Objective: present literature related to the pathophysiological mechanisms of Atrial Fibrillation, its impact on cardiovascular risk, and related aspects between angiotensin II and atrial fibrillation.

Methods: a non-systematic review of the available literature was conducted using key terms such as "Atrial Fibrillation" and "Angiotensin II", in addition to synonyms, which were combined with the "AND" and "OR" connectors, both in English and Spanish, in the PubMed, ScienceDirect, Embase, EBSCO, and MEDLINE databases.

Results: atrial fibrosis is a structural alteration that facilitates the maintenance of atrial fibrillation, Angiotensin II contributes to this process extensively by stimulating inflammatory processes, decreasing the activity of collagenase, increased expression of MAPK, and changes in cardiac electrophysiological properties through binding to the AT1 receptor.

Conclusions: getting to know the pathophysiology of atrial fibrillation at the molecular level, allows to further elucidate the context and possible complications of affected patients, facilitating the generation of hypotheses that contribute to the timely, accurate and effective diagnosis, the development of new therapeutic targets, as well as a better approach in the clinical area.

Keywords: Atrial Fibrillation; Renin-Angiotensin System; Angiotensin II; Cardiovascular Diseases; Cardiac Arrhythmias.
RESUMEN

Introducción: la fibrilación auricular es la arritmia más prevalente en el mundo y acarrea elevadas cifras de morbidad y mortalidad. Numerosos estudios han demostrado la participación del sistema renina angiotensina en la patogenia de la fibrilación auricular, y en varios de estos, se especula el mecanismo subyacente que involucra un proceso de remodelación del tejido auricular.

Objetivo: exponer literatura relacionada con los mecanismos fisiopatológicos de la Fibrilación Auricular, su impacto en el riesgo cardiovascular, y aspectos relacionados entre angiotensina II y fibrilación auricular.

Métodos: se llevó a cabo una revisión no sistemática de la literatura utilizando términos clave tales como “Atrial Fibrillation” y “Angiotensin II”, además de sinónimos, los cuales fueron combinados con los conectores “AND” y “OR”, tanto en inglés como en español, en las bases de datos PubMed, ScienceDirect, Embase, EBSCO, y MEDLINE.

Resultados: la fibrosis atrial constituye una alteración estructural que propicia el mantenimiento de la Fibrilación Auricular, y la Angiotensina II contribuye en este proceso ampliamente mediante la estimulación de procesos inflamatorios, disminución en la actividad de colagenasa, aumento en la expresión de MAPK, y cambios en las propiedades electrofisiológicas cardíacas a través de la unión al receptor AT1.

Conclusiones: conocer la fisiopatología de la fibrilación auricular a nivel molecular, permite dilucidar aún más el contexto y las posibles complicaciones de los pacientes afectados, facilitando la generación de hipótesis que contribuyan al diagnóstico oportuno, preciso y efectivo, el desarrollo de nuevas dianas terapéuticas, así como un mejor enfoque en el área clínica.

Palabras Clave: Fibrilación Auricular; Sistema Renina-Angiotensina; Angiotensina II; Enfermedades Cardiovasculares; Arritmias Cardiacas.

INTRODUCTION

Atrial Fibrillation (AF) is the most prevalent arrhythmia in the world, having high morbidity and mortality rates. In the United States between 3-5 million people present AF, and by 2050, the number is expected to rise above 8 million people (1). Numerous studies have shown the involvement of the angiotensin renin system (RAS) in the pathogenesis of AF, and in several of these, the underlying mechanism involving a process of atrial tissue remodeling is speculated (2).

AF is an arrhythmia caused by multiple factors that alter cardiac electrophysiological properties, and that produces re-entry circuits with changes in the electrical and structural properties of atrial tissue. Therapeutic options include pharmacological treatment, surgery, electrical cardioversion, and ablation therapy (3). Among the risk factors to develop AF, hypertension, aging, heart valve disease, obesity, diabetes, obstructive sleep apnea, cardiorespiratory disorders, and genetic load are highlighted (4-6).

Angiotensin II (AngII) constitutes the main peptide of the angiotensin renin system, widely known as a vasoactive agent for its effects at a local and systemic level. This is derived from a precursor produced at the hepatic level called angiotensinogen, through a process involving the enzymatic participation of renin (released by renal juxtaglomerular cells),
and the angiotensin-converting enzyme (ACE) (7,8). AngII acts by binding to its AT1 and AT2 receptors. The AT1 receptor is involved in metabolic pathways that mediate processes such as vasoconstriction, cell growth stimulation, connective tissue deposition, water retention, and increased renal sodium reabsorption.

On the other hand, the AT2 receptor is involved in metabolic pathways that mediate opposite effects to those promoted by AT1, such as vasodilation, decreased renal sodium reabsorption, inhibition of cell growth, and connective tissue deposition (9). Taking into consideration the burden of disease caused by atrial fibrillation, it is imperative to know the current evidence on the advances in its pathological description, as well as the therapeutic targets used for its management. Therefore, the objective of this manuscript is to present literature related to the pathophysiological mechanisms of AF, its impact on cardiovascular risk, and related aspects between angiotensin II and atrial fibrillation.

METHODS

A non-systematic review of the literature was conducted using key terms such as "Atrial Fibrillation" and "Angiotensin II", in addition to synonyms, which were combined with the "AND" and "OR" connectors, both in English and Spanish, in the PubMed databases, ScienceDirect, Embase, EBSCO, and MEDLINE. Observational and experimental studies were included, as well as narrative and systematic reviews of the literature with or without meta-analysis.

Finally, 61 potentially relevant articles were included, which provided evidence regarding the pathophysiology of angiotensin II-linked atrial fibrillation, as well as the diagnosis, prognosis and treatment of the same disease. During the review, which was carried out until July 2020, no specific updated literature on the topic was found.

RESULTS

Angiotensin-mediated atrial fibrillation-inducing molecular mechanisms

The renin-angiotensin system is an activated compensatory mechanism to regulate the homeostasis of the cardiovascular system, but its long-term effect can generate repercussions on the physiology of the individual. AF is characterized by the presence of electrical and structural alterations of atrial tissue along with fibrosis, this motive is the objective reason for evaluation in numerous studies, which have shown an increase in levels of Ang II and AT1 receptors, suggesting a close relationship between the angiotensin renin system, fibrosis and atrial fibrillation (10-15). Through a study carried out in murine models, in which two groups were evaluated, one treated with Ang II compared to one treated with saline solution, Jansen et al (16) found in the first group an increase in wall thickness and reduction of the internal diameter at the level of the left ventricle, added to an increase in the area corresponding to the left atrium, key data to show that Ang II produces hypertension, ventricular hypertrophy, and atrial enlargement. Likewise, they reported an extension in the duration of the p wave and the period of effective atrial refractory, thus illustrating that the time of conduction through the atria is slower in hearts treated with Ang II (16). Therefore, angiotensin II is categorized as a profibrotic agent that has a crucial role in atrial tissue remodeling in atrial fibrillation.

Atrial fibrosis is a structural alteration that promotes the maintenance of AF, and Ang II extensively contributes to this process by stimulating inflammatory processes, reducing collagenase activity, increasing the expression of MAPK, and changes in cardiac electrophysiological properties through the AT1 receptor binding (17). Among the inflammatory processes, Ang II contributes to the activation of NADPH oxidase and induces the generation of reactive oxygen species (ROS) in cardiac cells (18,19). Lu et al (20) demonstrated the increased production of ROS triggered by Ang II in myocytes of newborn mice, and additionally reported increased expression of AT1R, ACE,
angiotensigen, and Ang II due to hydrogen peroxide (20).

The transforming growth factor B1 (TGF-B1) mediates a signaling cascade within which it involves molecules such as PI3K/PAK2/Abl, through which it triggers the activity of pro-inflammatory nuclear transcription factors such as the nuclear factor Kappa B (NF-kB) (21,22). Additionally, phosphorylation of the TGF-B1 receptor participates in the activation of the MAPK signaling cascade, which controls the formation of fibroblasts and the synthesis of matrix metalloproteinases, being actively involved in the transition from endothelium to mesenchyme (23).

Studies in rabbits have demonstrated the inhibitory effect of AT1 receptor antagonists on TGF-B1 expression (24). The excessive collagen deposition resulting from the deregulation of the metabolism in the extracellular matrix leads to atrial fibrosis. Ge et al (25) identified MFGE8 as a regulatory molecule for atrial fibrosis because of its crucial role in inhibiting the TGFB-1/Smad2/Smad3 signaling pathway (25). Likewise, Tsai et al (26) demonstrated Ang II’s involvement in atrial structural remodeling through the Ang II/JAK/STAT3 pathway, which begins with the activation of STAT3 by Ang II through Rac1 in cardiac myocytes and fibroblasts.

The animal models underwent infusion with Ang II for a long time, presenting elevated levels of activated Rac1, phospho-STAT3, collagen synthesis, and fibrosis (26). Zheng et al (27) through studies in animal models and human samples, demonstrated the influence of Ang II during atrial remodeling, observing an increase in the expression of collagen type I and III, MMP1 and MMP2, increased phosphorylation of STAT3, caspase-3, caspase-8, cytochrome C transfer from mitochondria to the cytoplasm (involved in cell apoptosis); as well as cellular changes that decreased with the use of Losartan (27).

The structural remodeling distorts the nerve conduction velocity, due to the alteration in the coupling between the myocytes. Tanaka et al (28) demonstrated the role of Ang II in the automatism of the myocardium present in the pulmonary veins of an animal model, observing an increase in systolic depolarization thanks to an increase in the release of calcium from the sarcoplasmic reticulum, by activation of the IP3 receiver and activation of the Na+/Ca2+ exchanger (28). Following this order of ideas, it can be observed how the molecular description of the pathways linked to the pathological process of AF, facilitate the design of targeted targets in a specific way, and at the same time, they allow to predict possible complications that those affected by this condition presented.

Atrial fibrillation and cardiovascular risk

Within the broad field of factors that increase the incidence of cerebrovascular attack, atrial fibrillation is positioned as one of the main independent risk factors for the occurrence of ischemic stroke. AF is associated with major systemic thromboembolism and in approximately one-third of patients with ischemic stroke (Figure 1), the clinical or subclinical presentation of AF has been elucidated (29), as a result of a high prevalence of left atrial thrombosis (30).

Over the years, several scales have been implemented to stratify the risk in patients with atrial fibrillation and to contribute to decision-making for thromboprophylaxis. One of the risk stratification scales is CHADS2, which includes numerous items (congestive heart failure, hypertension, age over 75, diabetes mellitus, history of stroke or transient stroke) to which the value of 1 or 2 is assigned (depending on the severity) thus achieving a quantitative stratification of the risk of stroke at 12 months. The CHAD2VS2-VASc score adds a point for the following items: female sex, age 65-74 years (2 points if >75 years), and the presence of vascular disease. Ji et al (31) showed that the 1-point increase in CHADS2 score was associated with an increased risk of cardiovascular events and all-cause death (31). Another cutoff study in Israel showed that the 1-point increase in the CHADS2 score is associated with a 34% increase in the incidence of stroke in patients with atrial fibrillation (32).
In patients with AF, there is an over-activation of the clotting system, which generates a prothrombotic state as a result of blood stasis and platelet activation. Lee et al (33) by the means of 4D flow magnetic resonance, observed that the flow velocity in the left atrium of patients with atrial fibrillation in sinus rhythm was greater than in patients without sinus rhythm, but even so, the values persisted below those found in a similar age cohort with no history of atrial fibrillation. With these results, they postulated atrial remodeling as the cause of the reduced flow observed in patients with AF when they manifested sinus rhythm and additionally demonstrated an inverse relationship between the flow and the CHA2DS2-VASC score (33-35).

During AF, the ineffective contraction of the left atrium promotes vascular stasis, which, along with the pro coagulating state, produces an increase in the formation of thrombi at the level of the left atrial appendix, a remnant of sac-shaped embryonic development that would contribute to the cardiovascular risk of AF (36,37). Other prothrombotic abnormalities in patients with AF include alterations in the D-dimer, platelet factor-4, thrombin-antithrombin complexes, and plasminogen activator inhibitor (PAI-1). The ARISTOTLE study reported a significant association between D-dimer levels and the risk of stroke, cardiovascular death, and major hemorrhagic outcomes (38). Also, Claxton et al (39) found that in patients aged 75 years
or older with atrial fibrillation, and the presence of at least 3 comorbidities within which hypertension was the most prevalent, there was a significant increase in the risk for stroke, heart failure and bleeding, compared with patients without cardiometabolic comorbidities (39), so it can be concluded that the patient with AF and cardiometabolic abnormalities, will always have a higher risk than estimated.

Traditionally, the CHA2DS2-VASC score has been used for AF stratification, however, evidence suggests that serum biomarkers may be more useful in quantifying the risk of stroke in patients with AF. The most promising biomarkers are natriuretic peptides and cardiac troponins. The increase in serum troponin levels in patients with atrial fibrillation may reflect an ongoing myocardial lesion, and perhaps indicates more advanced pathological alterations of the atrium. In the RELY study, patients with persistent troponin I elevations were associated with an increased risk of thromboembolism or cardiac death (40).

Natriuretic peptides (atrial natriuretic peptide, cerebral natriuretic peptide) are synthesized in the myocytes of the atria and ventricles, in response to myocyte distension caused by a bulking or pressure surge. The mechanisms underlying the association between these biomarkers and the risk of stroke are not well established, however, it is speculated that they are related to the severity of comorbid conditions such as hypertension and heart failure (41). Some studies showed that high levels of BNP and NT-proBNP were linked to a higher incidence of AF (42,43). In the United States, in community studies covering a total of 18,556 patients, BNP and PCR levels were positively correlated with the incidence of atrial fibrillation (44). During a Framingham court evaluation, the NT-proANP connection with BNP was moderately high at 0.66, and after the incorporation of both natriuretic peptides into the model, BNP emerged as the strongest biomarker (45). In a sub-study of the ARISTOTLE trial, NT-proBNP levels were evaluated in almost 15,000 patients with nonvalvular atrial fibrillation, and those patients present in the highest quartile of NT-proBNP levels (>1250ng/l) were found, had an annual stroke rate of 2.2% compared to 0.7% for patients in the lowest quartile (46). Together these studies support the hypothesis that natriuretic peptides could be useful markers for estimating the risk of stroke, especially in those patients with a low CHA2DS2-VASC.

**Impact of pharmacological treatment on atrial fibrillation**

The angiotensin aldosterone renin system has a key role in the development of AF through the structural and electrical remodeling of atrial tissue, being the reason why numerous studies have investigated the efficacy of angiotensin-converting enzyme (ACE) inhibitors (47,48), angiotensin II receptor blockers (ARAII) (49,50) and aldosterone antagonists for the prevention and control of this condition (51).

Khatib et al (52) prepared a meta-analysis in which they included fourteen trials with 92,817 patients, evaluating the impact of angiotensin queen aldosterone inhibition compared to conventional or placebo therapy, in reducing new-onset atrial fibrillation. They showed that the ACE inhibitors showed little or no effect in the reduction of atrial fibrillation (RR= 0.79; 95% CI: 0.62-1.00, p-value: 0.05) compared to the ARA-II, which had a greater impact on this phenomenon (RR= 0.78; 95% CI: 0.66-0.92, p-value: 0.009). Aldosterone receptor antagonists did not play a role in the prevention of new-onset atrial fibrillation (RR= 0.77, 95% CI: 0.55-1.08, p-value: 0.21). Taken together, these results allowed them to conclude that inhibition of the angiotensin aldosterone system could contribute in part to the reduction of the risk of developing de novo AF (52). In a study based on the association of the use of SRA blockers and the development of AF in patients with myocardial infarction, Arslan et al (12) showed that the incidence of AF was low in those patients who had previous treatment with SRA blockers (69/965 patients) compared to untreated patients (12).

**New therapeutic targets**

From a pharmacological approach, the use of dual nepriplysin inhibitors and angiotensin receptors widely used in the treatment of heart failure have
shown benefits from the perspective of atrial fibrosis and atrial fibrillation. Neprilysin is a zinc-dependent metalloproteinase that cleaves peptides at the amino-terminal end of hydrophobic residues; it is mainly expressed in the kidney with which it was attributed participation in the degradation of atrial natriuretic peptide (53), and also in the brain associated with neural membranes (54).

In patients with cardiac failure, neprilysin levels are increased, thus improving the hydrolysis of atrial natriuretic peptides. Besides, it hydrolyses other vasoactive peptides such as a cerebral natriuretic peptide, bradykinin, substance P, oxytocin, angiotensin, among others (55). The PARADIGM-HF study showed that the use of dual neprilysin inhibitors and the angiotensin receptor could reduce morbidity and mortality in patients with heart failure with reduced ejection fraction (56). Likewise, other studies such as PARAGON-HF focused on determining the efficacy and safety of dual inhibitors in patients with heart failure and reduced ejection fraction, finding favorable results (57).

In a study that included 28 patients in the context of heart failure with reduced ejection fraction, Okutucu et al (58) found that the change of treatment from Valsartan to a dual neprilysin inhibitor and angiotensin receptor decreased the dispersion and maximum duration of the p-wave in the study subjects. One of the most frequent arrhythmias in heart failure is atrial fibrillation, which promotes left ventricle dysfunction, and this in turn triggers atrial remodeling and electrophysiological changes. The same researchers also found a reduction in NT-proBNP levels (r=0.460, p=0.014). They explained that possible anti-rhythmic effects of dual neprilysin inhibitors and angiotensin receptor might include clinical improvement, hemodynamic improvement (reduction of atrial wall stress mediated by natriuretic peptides or improvement in left ventricular function), reduction in myocardial fibrosis with which the substrate for atrial arrhythmias is altered, reduction of left ventricular hypertrophy, and improvement of autonomous cardiac functions (58,59). De Diego et al (60), conducted a study with 120 patients in the context of heart failure with reduced ejection fraction and implanted automatic defibrillator, showing that treatment with dual neprilysin inhibitors and angiotensin receptor decreased ventricular arrhythmias in patients with heart failure and reduced ejection fraction, compared to those that used angiotensin inhibitors in isolation. There was also a decrease in episodes of paroxysmal atrial fibrillation from 14% to 10%, without reaching statistical significance in the follow-up at 9 months (60).

A focus on the molecular mechanisms underlying the pathogenesis of fibrillation was carried out by Song et al (61), in which studies in animals and humans found elevated levels of EZH2, in the atrial muscle and atrial fibroblasts in patients with AF, accompanied by atrial fibrosis and local fibroblast differentiation. In vitro and in vivo experiments broke down the mechanism of action of EZH2, a molecule that regulates the differentiation of fibroblasts employing the Angiotensin II-TGF-B-Smad signaling pathway. In the same study, they discovered the GSK126 molecule as an inhibitor of angiotensin II-induced fibroblast differentiation and migration. In addition to pharmacological treatment, they achieved the molecular silencing of EZH2, thus blocking the differentiation of fibroblasts induced by angiotensin II, migration, and secretion of the extracellular matrix. These results formed the basis for considering the EZH2 molecule as a new therapeutic target for atrial fibrosis and AF (61).

**CONCLUSIONS**

Getting to know the pathophysiology of atrial fibrillation at the molecular level, allows to further elucidate the context and possible complications of affected patients, facilitating the generation of hypotheses that contribute to the timely, accurate and effective diagnosis, the development of new therapeutic targets, as well as a better approach in the clinical area. Basic research on this topic should be strengthened, since atrial fibrillation has a significant impact on the morbidity, mortality, and disability of the affected, and constitutes an independent risk factor for ischemic stroke. It is imperative to carry
out more studies, of the best quality, to be able to define with complete certainty the safety and efficacy of the molecules studied in past clinical trials, which present heterogeneous results. However, pharmacological treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and dual neprilysin inhibitors and angiotensin receptors can prevent and moderate the magnitude of this entity, so its use is supported by evidence of the best quality.

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