REVISTA CIENCIAS BIOMÉDICAS

ARTÍCULOS DE REVISIÓN

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

Andrés Elías Llamas Nieves[1], Ivan David Lozada-Martínez[1], Daniela Marcela Torres Llinás[1], Fernando Manzur Jattin[2], Miguel Cardales Periñán[3]

[1] School of Medicine, Medical-Surgical Research Center, University of Cartagena, Cartagena, Colombia.
[2] Basic Sciences Department, School of Medicine, Center of Biomedical Research, University of Cartagena, Colombia.
[3] School of Medicine, Center of Biomedical Research, University of Cartagena, Colombia.

ACCESO ABIERTO

Para citaciones: Llamas, A., Lozada, I., Torres, D., Manzur, F., Cardales, P. (2021). News on angiotensin II and atrial fibrillation: from the molecular to the pathophysiological. Revista Ciencias Biomédicas, 10(2), 109-119. https://doi.org/10.32997/rcb-2021-3371

Recibido: December 13th, 2020
Aprobado: March 3rd, 2021

Autor de correspondencia:
Ivan David Lozada-Martínez
ivandavidloma@gmail.com

Editor: Inés Benedetti. Universidad de Cartagena-Colombia.

Copyright: © 2021. Llamas, A., Lozada, I., Torres, D., Manzur, F., Cardales, P. Este es un artículo de acceso abierto, distribuido bajo los términos de la licencia https://creativecommons.org/licenses/by-nc-sa/4.0/ la cual permite el uso sin restricciones, distribución y reproducción en cualquier medio, siempre y cuando el original, el autor y la fuente sean acreditados.

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 morbilidad 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 and 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,

angiotensinogen, 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 CHAD2DS2-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).

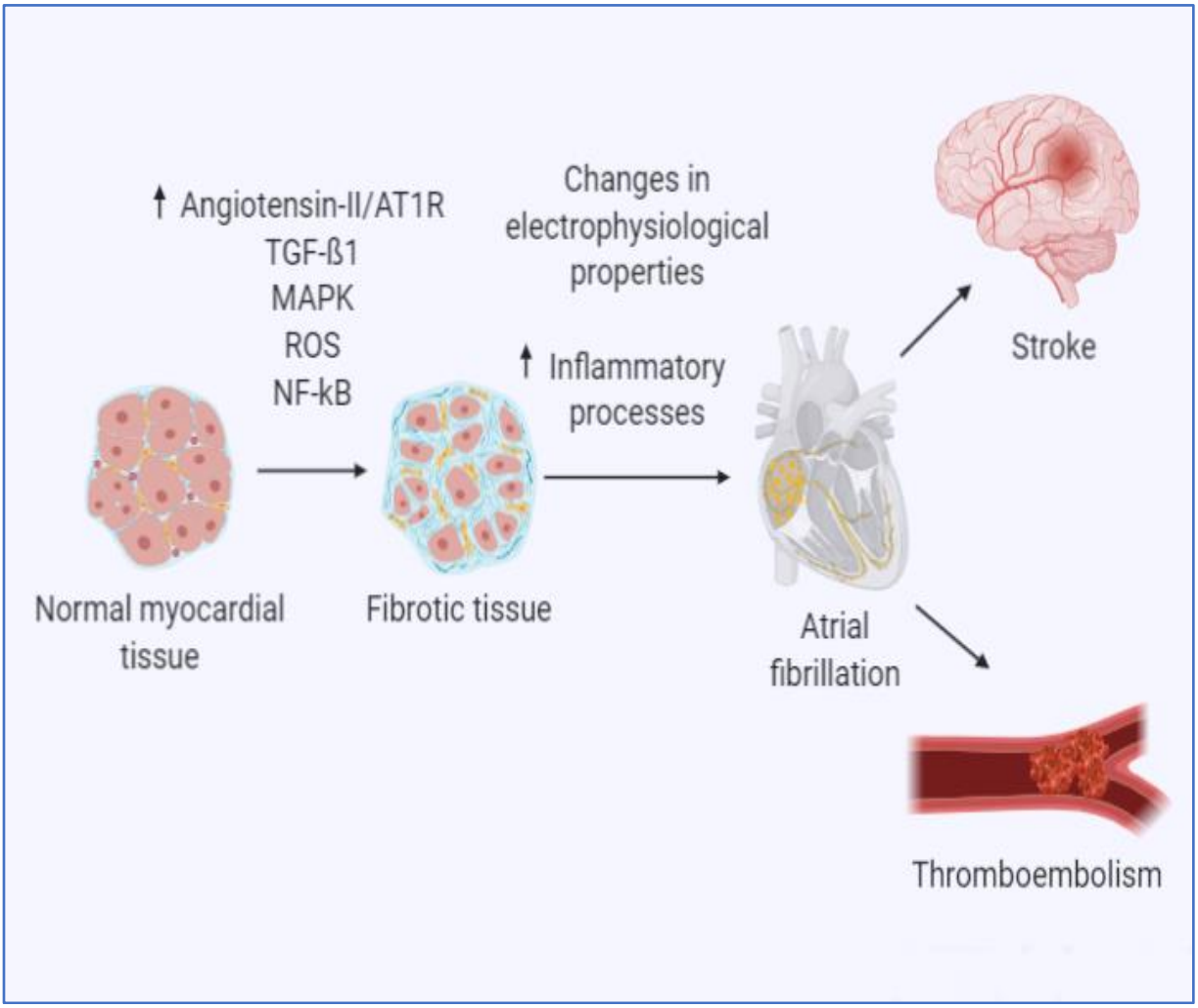

Figure 1. Graphic representation of the impact of angiotensin II-induced myocardial fibrosis, causing atrial fibrillation secondary to changes in cardiac electrophysiological properties, due to the persistence of local inflammatory processes, increasing the risk of developing ischemic stroke and systemic thromboembolism. Created with BioRender.

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 neprilysin 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.

AUTHORS CONTRIBUTIONS: conception and design of the study: ALL, DT, FM and MC. Collection, analysis and interpretation of data: ALL, IL and DT. Writing the draft of the article: ALL, IL and DT. Critical review and final version approval: ALL, IL, DT, FM and MC. Responsible for the veracity and integrity of the article: IL, FM and MC.

REFERENCES

1. Zuljifly H, Lip G, Lane D. Epidemiology of atrial fibrillation. International Journal of Clinical Practice. 2018; 72(3): e13070.

2. Shivshankar T, Lau D, Agbaedeng T, Elliott D, Mahajan R, Sanders P. Molecular mechanisms of atrial fibrosis: implications for the clinic. Expert Rev Cardiovasc Ther. 2017; 15(4): 247-256.

3. Lip GY, Tello-Montoliu A. Management of atrial fibrillation. Heart. 2006; 92(8): 1177-82.

4. Lau DH, Middeldorp ME, Brooks AG, Ganesan AN, Roberts-Thomson KC, Stiles MK, et al. Aortic stiffness in lone atrial fibrillation: a novel risk factor for arrhythmia recurrence. PLoS One. 2013; 8(10): e76776.

5. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. J Am Coll Cardiol. 2015; 66(9): 985-96.

6. Tucker NR, Clauss S, Ellinor PT. Common variation in atrial fibrillation: navigating the path from genetic association to mechanism. Cardiovasc Res. 2016; 109(4): 493–501.

7. Mascolo A, Urbanek K, De Angelis A, Sessa M, Scavone C, Berrino L, et al. Angiotensin II and angiotensin 1-7: which is their role in atrial fibrillation?. Heart Fail Rev. 2020; 25(2): 367-380.

8). Wagner P. Pathophysiology of hypertension: new concepts. Rev Peru Ginecol Obstet. 2018; 64(2): 175-184.

9. Nehme A, Zouein FA, Zayeri ZD, Zibara K. An Update on the Tissue Renin Angiotensin System and Its Role in Physiology and Pathology. J Cardiovasc Dev Dis. 2019; 6(2): 14.

10. Kishihara J, Niwano S, Niwano H, Aoyama Y, Ishikawa S, Oikawa J, et al. Long-term observation of fibrillation cycle length in patients under angiotensin II receptor blocker therapy for chronic atrial fibrillation. Journal of Arrhythmia. 2012; 28: 34-40.

11. Fauchier L, de Groote P. Atrial fibrillation and renin-angiotensin-aldosterone system: believe it or not. Europace. 2011; 13(3): 297-8.

12. Arslan A, Ozaydin M, Aksoy F, Arslan B, Aydin H, Erdogan D, et al. Association between the use of renin-angiotensin system blockers and development of in-hospital atrial fibrillation in patients with ST-segment elevation myocardial infarction. Medicina. 2016; 52(2): 104-109.

13. Seccia T, Caroccia B, Muiesan M, Rossi G. Atrial fibrillation and arterial hypertension: A common duet with dangerous consequences where the renin angiotensin-aldosterone system plays an important role. International Journal of Cardiology. 2016; 206: 71-76.

14. Lugenbiel P, Wenz F, Govorov K, Syren P, Katus H, Thomas D. Atrial myofibroblast activation and connective tissue formation in a porcine model of atrial fibrillation and reduced left ventricular function. Life sciences. 2017; 181: 1-8.

15. Nair GM, Nery PB, Redpath CJ, Birnie DH. The Role of Renin Angiotensin System In Atrial Fibrillation. J Atr Fibrillation. 2014; 6(6): 972.

16. Jansen H, Mackasey M, Moghtadaei M, Belke D, Egom E, Tuomi J, et al. Distinct patterns of atrial electrical and structural remodeling in angiotensin II mediated atrial fibrillation. J Mol Cell Cardiol. 2018; 124: 12-25.

17. Perlini S, Belluzzi F, Salinaro F, Musca F. Atrial Fibrillation - Mechanisms and Treatment [Internet]. Tong Liu; 2013. [Consulted 5 Nov 2020]. Available in: https://www.intechopen.com/books/atrial-fibrillation-mechanisms-and-treatment/atrial-fibrillation-and-the-renin-angiotensin-aldosterone-system

18. Youn J, Zhang J, Zhang Y, Chen H, Liu D, Ping P, et al. Oxidative stress in atrial fibrillation: an emerging role of NADPH oxidase. J Mol Cell Cardiol. 2013; 62: 72-79.

19. Lu G, Xu S, Peng L, Huang Z, Wang Y, Gao X. Angiotensin II upregulates Kv1.5 expression through ROS-dependent transforming growth factor-beta1 and extracellular signal-regulated kinase 1/2 signalings in neonatal rat atrial myocytes, Biochem Biophys Res Commun. 2014; 454(3): 410-416.

20. Lu G, Xu C, Tang K, Zhang J, Li Q, Peng L. H2S inhibits angiotensin II-induced atrial Kv1.5 upregulation by attenuating Nox4/mediated EOS generation during atrial fibrillation. Biochem Biophys Res Commun. 2016; 483(1): 1-7.

21. Bujor AM, Asano Y, Haines P, Lafyatis R, Trojanowska M. The c-Abl tyrosine kinase controls protein kinase Cδ-induced Fli-1 phosphorylation in human dermal fibroblasts. Arthritis Rheum. 2011; 63(6): 1729-37.

22. Piera-Velazquez S, Li Z, Jimenez SA. Role of Endothelial- Mesenchymal Transition (EndoMT) in the pathogenesis of fibrotic disorders. Am J Pathol. 2011; 179(3): 1074–1080.

23. Lamouille S, Derynck R. Emergence of the phosphoinositide 3- kinase-Akt-mammalian target of rapamycin axis in transforming growth factor-β-induced epithelial-mesenchymal transition. Cells Tissues Organs. 2011; 193(1–2): 8–22.

24. He X, Gao X, Peng L, Wang S, Zhu Y, Ma H, et al. Atrial fibrillation induces myocardial fibrosis through angiotensin II type 1 receptor-specific Arkadia-mediated downregulation of Smad7. Circ Res. 2011; 108(2): 164-75.

25. Ge Z, Chen Y, Wang B, Zhang X, Yan Y, Zhou L, et al. MFGE8 attenuates Ang-II-induced atrial fibrosis and vulnerability to atrial fibrillation through inhibition of TGF-β1/Smad2/3 pathway. J Mol Cell Cardiol. 2020; 139: 164-175.

26. Tsai CT, Lai LP, Kuo KT, Hwang JJ, Hsieh CS, Hsu KL, et al. Angiotensin II activates signal transducer and activators of transcription 3 via Rac1 in atrial myocytes and fibroblasts: implication for the therapeutic effect of statin in atrial structural remodeling. Circulation. 2008; 117(3): 344-55.

27. Zheng L, Jia X, Zhang C, Wang D, Cao Z, Wang J, et al. Angiotensin II in atrial structural remodeling: the role of Ang II/JAK/STAT3 signaling pathway. Am J Transl Res. 2015; 7(6): 1021-31.

28. Tanaka Y, Obata K, Ohmori T, Ishiwata K, Abe M, Hamaguchi S, et al. Angiotensin II induces automatic activity of the isolated Guinea Pig pulmonary vein myocardium through activation of the IP3 receptor and the Na+-Ca2+ exchanger. Int J Mol Sci. 2019; 20(7): 1768.

29. Freedman B, Potpara TS, Lip GYH. Stroke prevention in atrial fibrillation. Lancet. 2016; 388(10046): 806-817.

30. Fadhlullah AA, Abdalgbar AA, Altalhi HK. Non rheumatic atrial fibrillation as risk of stroke. Am J Internal Med. 2016; 4(6): 117.

31. Ji C, Wu S, Shi J, Huang Z, Chen S, Wang G. Baseline CHADS2 score and risk of cardiovascular events in the population without atrial fibrillation. The American Journal of Cardiology. 2020; 129: 30-35.

32. Saliba W, Gronich N, Barnett-Griness O, Rennert G. The role of CHADS2 and CHA2 DS2 -VASc scores in the prediction of stroke in individuals without atrial fibrillation: a population-based study. J Thromb Haemost. 2016; 14: 1155–1162.

33. Lee D, Goldberger J, Fluckiger J, Ng J, Carr J, Collins J, et al. Analysis of left atrial flow velocity distribution by 4D flow MRI in patients with atrial fibrillation. Circulation. 2013; 128: A17900.

34. Lee D, Markl M, Ng J, Carr M, Benefiled B, Carr J, et al. Atrial fibrillation is associated with altered left atrial 3D hemodynamics and increased stasis. Circulation. 2014; 130: A14026.

35. Goldberger J, Fluckiger J, Lee D, Ng J, Olsen AB, Carr J, et al. Left atrial flow velocity distribution in atrial fibrillation by 4D flow MRI: A new marker for risk of stroke? Heart Rhythm. 2013; 10: S384.

36. Siontis K, Geske J, Gersh B. Atrial fibrillation pathophysiology and prognosis insights from cardiovascular imaging. Circ Cardiovasc Imaging. 2015; 8(6): e003020.

37. Goldberger J, Arora R, Green D, Greenland P, Lee D, Lloyd D, et al. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. Circulation. 2015; 132(4): 278-291.

38. Christersson C, Wallentin L, Andersson U, Alexander JH, Ansell J, De Caterina R, et al. D-dimer and risk of thromboembolic and bleeding events in patients with atrial fibrillation--observations from the ARISTOTLE trial. J Thromb Haemost. 2014; 12: 1401-1412.

39. Claxton J, Chamberlain A, Lutsey P, Chen L, MacLehose R, Bengston L, et al. Association of multimorbidity with cardiovascular endpoints and treatment effectiveness in patients 75 years and older with atrial fibrillation. The American Journal of Medicine. 2020; 133(10): e554-e567.

40. Hijazi Z, Oldgren J, Andersson U, Connolly SJ, Ezekowitz MD, Hohnloser SH, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation. 2012; 125:1605–1616.

41. Rubattu S, Volpe M. Natriuretic peptides in the cardiovascular system: multifaceted roles in physiology, pathology and therapeutics. Int J Mol Sci. 2019; 20(16):3991.

42. Patton KK, Heckbert SR, Alonso A, Bahrami H, Lima JA, Burke G, et al. N-terminal pro-B-type natriuretic peptide as a predictor of incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis: The effects of age, sex and ethnicity. Heart. 2013; 99: 1832–1836.

43. Svennberg E, Lindahl B, Berglund L, Eggers KM, Venge P, Zethelius B, et al. NT-proBNP is a powerful predictor for incident atrial fibrillation—Validation of a multimarker approach. Int J Cardiol. 2016; 223: 74–81.

44. Sinner MF, Stepas KA, Moser CB, Krijthe BP, Aspelund T, Sotoodehnia N, et al. B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: The CHARGE-AF Consortium of community-based cohort studies. Europace. 2014; 16: 1426–1433.

45. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. Circulation, 2010; 121: 200–207.

46. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, Christersson C, Ezekowitz J, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation). J Am Coll Cardiol. 2013; 61: 2274–2284.

47. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B, et al. Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol: The Losartan Intervention for end Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol. 2005; 45: 712–9.

48. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation. 1999; 100(4): 376–80

49. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008; 372(9644): 1174–83.

50. Dahl JS, Videbaek L, Poulsen MK, Pellikka PA, Veien K, Andersen LI, et al. Effect of candesartan treatment on left ventricular remodeling after aortic valve replacement for aortic stenosis. Am J Cardiol. 2010; 106(5): 713–9.

51. Swedberg K, Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Shi H, et al. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure) study. J Am Coll Cardiol. 2012; 59(18): 1598-603.

52. Khatib R, Joseph P, Briel M, Yusuf S, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of

randomized controlled trials. Int J Cardiol. 2013; 165(1): 17-24.

53. Carson JA, Turner AJ. Beta-amyloid catabolism: Roles for neprilysin (nep) and other metallopeptidases?. J Neurochem. 2002; 81: 1-8.

54. Barnes K, Turner AJ, Kenny AJ. Membrane localization of endopeptidase-24.11 and peptidyl dipeptidase a (angiotensin converting enzyme) in the pig brain: A study using subcellular fractionation and electron microscopic immunocytochemistry. J Neurochem. 1992; 58: 2088-2096.

55. Stephenson SL, Kenny AJ. Metabolism of neuropeptides. Hydrolysis of the angiotensins, bradykinin, substance p and oxytocin by pig kidney microvillar membranes. Biochem J. 1987; 241: 237-247.

56. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11): 993-1004.

57. Solomon S, Rizkala A, Gong J, Wang W, Anand I, Ge J, et al. Angiotensin receptor neprilisyn inhibition in heart failure with preserved ejection fraction: Rationale and design of the PARAGON-HF Trial. JACC Heart Fail. 2017; 5(7): 471-482.

58. Okutucu S, Fatihoglu SG, Sabanoglu C, Bursa N, Sayin BY, Aksoy H, et al. Effects of angiotensin receptor neprilysin inhibition on P-wave dispersion in heart failure with reduced ejection fraction. Herz. 2019.

59. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015; 36(30): 1990–1997.

60. De Diego C, Gonzalez-Torres L, Nunez JM, Centurion Inda R, Martin-Langerwerf DA, Sangio AD, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhytm. 2018; 15(3): 395-402.

61. Song S, Zhang R, Mo B, Chen L, Liu L, Yu Y, et al. EZH2 as a novel therapeutic target for atrial fibrosis and atrial fibrillation. J Mol Cell Cardiol. 2019; 135: 119-133.