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Editorial

Diagnostic and therapeutic potential of miRNAs in cardiovascular disease: a clinical reality?

Valor diagnóstico y terapéutico de los microARN en patología cardiovascular: ¿una realidad en la clínica?

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The year 2023 will mark the 30th anniversary of the discovery of the first microRNA (miRNA): lin-4. MiRNAs are short (~22 nucleotides) noncoding RNAs, which are highly preserved and single-stranded, and which influence a multitude of biological processes. Each miRNA is capable of regulating a large number of target genes by inhibiting messenger RNA translation or inducing its degradation.[1] Since their first description, hundreds of miRNAs have been discovered with key roles in gene regulation.

In recent years, miRNAs have received increasing attention as diagnostic biomarkers due to evidence of their potential role in the pathogenesis of neurological, oncological, and cardiovascular diseases. Indeed, it is known that over- or under-expression of miRNAs can contribute to the development of cardiovascular diseases, including atrial fibrillation (AF).[2] However, the underlying mechanisms of AF are extremely complex, and several risk factors are implicated in this arrhythmia, importantly, many of them modifiable. As there is still room for exploration in AF, further contributions that shed light on novel risk factors beyond traditional ones and their influence on AF are essential to improve therapies and outcomes.

Several functions suggest a role for miRNAs in AF pathophysiology through the regulation of remodelling mechanisms, such as electrical, structural and autonomic nerve remodelling, fluctuations in calcium levels, and inflammation.[3] However, their use as a biomarker for the diagnosis and prediction of AF is still questionable.

One of the most studied miRNAs in AF is miR-1, which is expressed in cardiac and skeletal muscles and is associated with electrical remodelling by decreasing the concentration of intracellular calcium ions, increasing the risk of developing cardiac arrhythmias.[4] In addition, revealing its nonspecific character, many studies have also shown that aberrant levels of miR-1 play an important role in the initiation, development and metastasis of cancers such as lung, liver, colorectal, pancreatic, medulloblastoma, gastric, and prostate cancer.[5] Other functional miRNAs involved in AF are miR-328, also implicated in electrical remodelling through targeting L-type Ca^{2+}channel genes,[6] and miR-21, whose overexpression has been reported to enhance mitogen-activated protein kinase pathway signalling in cardiac fibroblasts, leading to their proliferation and resulting in cardiac fibrosis and remodelling.[7]

In a recent article published in *Revista Española de Cardiología*, Benito et al.[8] present the results of a prospective cohort of 64 patients divided into 2 groups with follow-up at 6 and 12 months. The first group included patients with cryptogenic stroke (CrS) and sinus rhythm (SR) (CrS-SR; n = 36), while the second was composed of patients with CrS and AF (CrS-AF; n = 28). The authors selected 9 patients from each group, and a further new group of 9 patients with cardioembolic stroke and AF (CES-AF) was included as a guide for miRNA selection. The authors initially measured 854 miRNAs in plasma and finally they selected 16 of them due to significant differences between groups 1 and 2. Then, 8 miRNAs were selected as potential candidates due to their differential expression between CrS-AF and CES-AF patients compared with controls, and 5 of them (miR-744-5p, miR-1-3p, miR-377-3p, miR-425-5p and miR-19b-3p) were also significantly different between CrS-SR and CES-AF patients. Therefore, the authors proposed these as potential indicators of a predisposing milieu for AF. Finally, only plasma miR-1-3p levels remained significantly elevated in CrS-AF vs CrS-SR patients (2.81-fold increase; $P = .014$). Hence, the researchers linked the possible involvement of miRNA-1-3p in patients with CrS and AF.[8] This is an interesting study based on a nontargeted miRNA analysis in a selected series of patients, which reveals novel miRNAs with possible involvement in AF.

However, there are still some controversial issues. Previous evidence shows that mRNA-1-3p is implicated in cardiac arrhythmogenesis but it is also deregulated in bladder cancer,[9] lung cancer,[10] and prostate cancer.[11] A recent article demonstrated that miR-425-5p, one of the miRNAs in which differences were detected between CES-AF and CrS-SR patients by Benito et al.,[8] was down-regulated in the plasma and atrial tissue of AF patients.[12]

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Therefore, more studies are needed to elucidate the role of these miRNAs in the pathophysiology of AF.

Hence, the remaining question is: how does this information translate into everyday clinical practice? There are some obstacles to assessing miRNAs that are often difficult to overcome. Factors such as the time required to obtain miRNA sequencing results, as well as the ability to handle data relating to around 900 miRNAs, as measured by Benito et al.,[8] make it difficult to establish this type of screening as standard practice. Moreover, the management of AF includes taking decisions in (sometimes) very busy clinics and with limited resources. For example, most AF patients will require oral anticoagulants for stroke prevention, and this decision, particularly in secondary prevention, should be made as soon as possible to avoid potential exposure to a higher risk of thromboembolism. Thus, the usefulness of miRNAs in this context is at least limited.

As AF is the most prevalent arrhythmia worldwide, the lack of availability of an miRNA assay and the required equipment means that it cannot be widely used and cannot be a reality in smaller hospitals, primary care centers, isolated health institutions, or in countries with lower income levels, leading to a large bias in diagnosis. The clear limitation of a single determination should be also addressed. Last but not least, there is the high cost to the health care system as well as inter- and intra-assay variability, which hinders miRNA use in everyday clinical practice.

Finally, the mechanisms involved in AF must be considered in conjunction with other risk factors such as obesity, hypertension, diabetes, sleep apnoea and the state of systemic inflammation, which in turn determine a higher AF substrate.[13] Indeed, the management of AF has evolved substantially in the last few years, moving toward a more integrated and holistic management addressing modifiable cardiovascular risk factors and comorbidities, as part of the Atrial fibrillation Better Care pathway.[14] Such an approach has been included in the 2020 European Society of Cardiology AF guidelines,[15] and leads to a notable reduction in the risk of adverse outcomes.

Thus, it is recognized that focusing on modifiable risk factors is central for AF management and directly translates into a lower risk of new-onset AF, recurrence of AF and worse clinical outcomes, while miRNAs are a genetic marker that cannot be addressed. In summary, miRNAs are promising biomarkers, but we are still far from their routine clinical application. Knowing more about how miRNAs are integrated into heart disease is a fundamental requisite for their development as potential therapeutic targets.

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CONFLICTS OF INTEREST

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