Nature Communications: Spanish scientists discover a possible treatment for a heart condition that causes an estimated 20% of sudden deaths among athletes

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This disease, which can trigger sudden death in elite athletes, is caused by genetic mutations that affect proteins responsible for connecting and coordinating the muscle cells (myocytes) in the myocardium the heart's muscular wall

A team of researchers at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) has discovered a possible treatment for a disease that causes sudden death in athletes. Arrhythmogenic cardiomyopathy is an incurable disease of the heart muscle that is responsible for an estimated 20% of sudden deaths recorded in professional athletes.

The CNIC team, led by Dr. Juan A. Bernal, who heads the CNIC Viral Vectors Unit, has discovered a treatment that restores the contractile capacity of the myocardium in animal models of arrhythmogenic cardiomyopathy.

The researchers investigated mutations in the protein plakofilin-2 (PKP2) that cause arrhythmogenic cardiomyopathy and discovered a previously unknown function of PKP2, a protein that controls the functional connections between myocytes in the heart. The results are published in the journal *Nature Communications*.

Arrhythmogenic cardiomyopathy has two major clinical manifestations, cardiac contraction defects and malign ventricular arrhythmias. These can cause loss of consciousness and even sudden death, often linked to episodes of intense physical activity.

Lead investigator Juan A. Bernal explained that the study "focuses on the contraction defect in this disease. Through this approach, we have been able to discover the reason the myocytes do not contract sufficiently and identify a way to solve this problem. Understanding the mechanisms of this disease is an essential step toward developing new treatments."

Scientists have reported more than 350 mutations in PKP2, "but we don't know which ones cause disease or how aggressive they are," said Bernal. "What we have known for several years is that intense physical exercise accelerates the development of the disease."

While there is still a long way to go to fully define the molecular basis of arrhythmogenic cardiomyopathy, the current study identifies a group of mutations that are consistently associated with severe contractile problems that respond to treatment with an activator of myosin regulators called 4-hydrozyacetophenone (4-HAP).

"Our results provide proof of concept that the generation of a complete atlas of all PKP2 mutations can help to stratify the risk of patients with arrhythmogenic cardiomyopathy so that sudden deaths, like the famous case of Sevilla FC player Antonio Puerta, who died in 2007, can be prevented in the future," said Dr. Nieves García-Quintáns, the first author on the study.

"Our quest for treatments for this terrible disease that preys on young athletes would have been impossible without the public–private funding from the CNIC and the support of the Ministerio de Ciencia, Innovación y Universidades, the "la Caixa" Foundation, and Real Madrid Graduate School - Universidad Europea. We are also keen to establish contacts with other clubs that might be interested in supporting our research," added Dr. Bernal.

The full Imaris analysis was conducted by the CNIC Microscopy and Dynamic Imaging Unit (ICTS-ReDib), which is cofinanced by Ministerio de Ciencia e Innovación (MCIN).

- *García-Quintáns N, Sacristán S, Márquez-López C, Sánchez-Ramos C, Martinez-de-Benito F, Siniscalco D, González-Guerra A, Camafeita E, Roche-Molina M, Lytvyn M, Morera D, Guillen MI, Sanguino MA, Sanz-Rosa D, Martín-Pérez D, Garcia R, Bernal JA. MYH10 activation rescues contractile defects in arrhythmogenic cardiomyopathy (ACM). Nat Commun. 2023 Oct*

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