Nature Cardiovascular Research: Researchers uncover a new mechanism underlying the most common inherited heart disease and confirm the effectiveness of a next-generation therapy

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A study led by the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), working in collaboration with an international research team, has identified a new molecular mechanism involved in hypertrophic cardiomyopathy, the most common inherited cardiovascular disease.

The research, published in *Nature Cardiovascular Research*, also demonstrates that mavacamten—the first targeted therapy available for this condition—is effective across different types of genetic mutations.

Hypertrophic cardiomyopathy is the most common inherited heart disease and the leading cause of sudden cardiac death in young people and athletes. According to epidemiological data from the Spanish Heart Foundation and the Spanish cardiovascular research network (CIBERCV), the condition affects approximately 1 in every 250 to 500 people in the general population. In Spain, an estimated 95,230 individuals are living with this disease.

The disease is characterized by abnormal thickening of the heart muscle (hypertrophy) and excessive contraction (hypercontractility) of cardiomyocytes, the cardiac muscle cells responsible for generating force with each heartbeat. The thickening can obstruct blood flow out of the heart, while the abnormally forceful contractions can disrupt normal rhythm, in severe cases fatally.

Hypertrophic cardiomyopathy is caused by mutations in genes encoding sarcomere proteins, the molecular machinery of the heart. Among these, the MYBPC3 gene, which encodes cardiac myosin binding protein C (cMyBP C), is one of the most frequently implicated.

The new study provides an important advance in understanding the disease. “Our work focuses on the molecular mechanism of a subgroup of MYBPC3 mutations that, unlike the most common mutation types, do not reduce protein levels but instead alter its ability to interact with other cardiac proteins,” explains Laura Sen Martín, first author of the study. “Until now, the precise mechanism through which these mutations cause disease was not well defined.”

To address this question, the team introduced the R502W variant of cMyBP C into mice, generating an animal model that reproduces key features of the disease. Analysis of this model revealed that the mutation reduces the ability of cMyBP C to interact with myosin, the molecular motor responsible for heart contraction. According to the authors, this disruption represents a newly identified pathogenic mechanism for this subgroup of patients.

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Given that the R502W mutation triggers molecular events distinct from those seen in other mutation types, the CNIC team evaluated the efficacy of mavacamten—the only targeted drug currently available for hypertrophic cardiomyopathy—in the new mouse model.

Mavacamten acts on myosin, modulating its activity and reducing excessive cardiac contractility. The results showed that treatment halted pathological remodeling of the heart muscle in both the R502W model and in a model with complete loss of cMyBP C. However, only the R502W mice showed improved exercise tolerance.

The drug also proved effective in laboratory-generated human cardiac tissue derived from induced pluripotent stem cell-derived cardiomyocytes, where it reduced the excessive contractile force of diseased tissue. These findings further support the potential clinical relevance of the results.

“Mavacamten and related molecules are transforming the treatment of patients with hypertrophic cardiomyopathy; however, not all patients respond in the same way,” explains lead author Dr. Jorge

Alegre Cebollada, head of the CNIC Molecular Mechanics of the Cardiovascular System Group and a researcher with CIBERCV. “Our study suggests that this variable effectiveness is not due to the different mutations carried by patients.”

Overall, the study confirms that mavacamten is effective regardless of the molecular mechanism underlying disease development, expanding the spectrum of patients who may benefit from treatment. In addition, the newly developed mouse model represents a valuable tool for testing future targeted therapies for this subgroup of patients. “For example, our experimental model can be used to explore whether early administration of mavacamten improves therapeutic outcomes, an important question that remains unresolved in the clinical setting,” concludes Laura Sen Martín.

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