New test successfully identifies life-threatening heart disease

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A study led by investigators at Beth Israel Deaconess Medical Center (BIDMC) has demonstrated that a new immunohistochemical test is reliable in diagnosing a dangerous arrhythmic heart disease known as arrhythmogenic right ventricular cardiomyopathy (ARVC.) Reported in the March 12 issue of The *New England Journal of Medicine* (*NEJM*), the new findings offer the possibility of a highly sensitive and specific means of identifying this life- threatening condition at an early stage, when it can be treated with by implanting a cardiac defibrillator.

"In many individuals, ARVC has no symptoms or warning signs, meaning that the first and only manifestation of disease is sudden death," explains the study's senior author Jeffrey E. Saffitz, MD, PhD, Chairman of the Department of Pathology at BIDMC and Mallinckrodt Professor of Pathology at Harvard Medical School. The hereditary condition, which affects approximately 1 in 5,000 individuals worldwide, is particularly prevalent among Mediterranean populations and, in Italy, is the leading cause of sudden cardiac death among patients under age 35.

ARVC affects the muscle of the heart's right ventricle (one of the organ's two main pumping chambers) so that, over time, muscle cells become replaced by fatty deposits and fibrosis, leaving the right ventricle especially susceptible to arrhythmias. Once an arrhythmia develops, the heartbeat becomes rapid and erratic causing the victim to grow dizzy or collapse -- and in the most serious cases to suffer sudden cardiac death.

"ARVC has been linked to genetic mutations in proteins that form desmosomes, subcellular structures responsible for cell-to-cell adhesion," explains Saffitz, whose laboratory studies connections between cells in the heart and their relationship to arrhythmias and sudden cardiac death. Several years ago, he and his colleagues discovered that a desmosomal protein known as plakoglobin was dramatically diminished in tissue samples of ARVC. In this new study, the authors set out to determine if this reduced plakoglobin signal could serve as a biomarker for ARVC early in the course of the disease.

After ascertaining that the protein was indeed diminished in cases of ARVC -- and not from other types of heart disease -- the authors performed "blinded" immunohistochemical analysis of heart-biopsy samples, obtained from an ARVC registry located at Johns Hopkins University School of Medicine.

The results were remarkably accurate.

"On the basis of clinical criteria, we made the correct diagnosis in 10 of 11 subjects with definite ARVC and correctly ruled out ARVC in 10 of 11 subjects who did not have the condition," explains Saffitz. "There was no question that the plakoglobin signal level was reduced diffusely in the ARVC samples."

Although previous studies have found that magnetic resonance imaging (MRI), electrocardiography and echocardiography can accurately identify patients with advanced AVRC, these tests are much less sensitive for patients with earlier or less conspicuous disease, notes Saffitz.

"An immunohistochemical test [based on plakoglobin levels] could, in the future, provide clinicians with an important new diagnostic tool," he adds. "Cardiologists at major medical centers in the U.S. routinely

evaluate cases of unexplained arrhythmias, and this new test may help them to identify ARVC in some of these patients and to exclude it as a cause of arrhythmias in others.

"Additional work will be necessary to validate this new test but it holds considerable promise in identifying people at risk of sudden death in whom preventive measures such as placement of an internal defibrillator may be life-saving," says Saffitz.

BIDMC has filed patents covering methods of diagnosing ARVC.

Source: Beth Israel Deaconess Medical Center