

# Cardiomyopathy: Genetics, Diagnosis, and Treatment

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Arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited myocardial disorder, is associated with arrhythmias, heart failure, and sudden death [Syrris P et al. *Am J Hum Genet* 2006; Yang Z et al. *Circulation Res* 2006]. Clinical diagnosis of ARVC can be complicated, because multiple diagnostic tests are required and clinical presentation varies. William McKenna, MD, University College London, London, UK, discussed the etiology of ARVC and recent breakthroughs concerning detection.

Desmosomes consist of several proteins that serve as specialized intercellular junctions of the cardiac and endothelial tissue that are involved in cell-to-cell adhesion and intracellular signaling. ARVC is a genetic disorder that involves desmosomal mutations, particularly in the desmoplakin, N-cadherin, and plakoglobin pathways. Within single families that carry these mutations, there are variations in ARVC presentation, such as age at onset, clinical features, and outcomes [Bauce B et al. *Eur Heart J* 2005; Norman M et al. *Circulation* 2005; Kannankeril PJ et al. *Heart Rhythm* 2006; Syrris P et al. *Eur Heart J* 2007].

In a recent study by Asimaki and colleagues, routine immunohistochemical analysis of endomyocardial biopsy samples revealed high sensitivity (91%) and specificity (82%) for ARVC diagnostic testing (Table 1). Ten of 11 subjects were correctly diagnosed with ARVC based on clinical criteria, and ARVC was accurately ruled out in 10 of 11 subjects without ARVC (positive predictive value 83% and negative predictive value 90%; Figure 1) [Asimaki A et al. *N Engl J Med* 2009]. Prof. McKenna concluded that these recent findings and ongoing genetic studies may have practical implications for ARVC detection in the clinical setting.

**Table 1. Clinical and Immunohistological Diagnoses in Blinded Analysis of Cardiac Biopsy Specimens.**

Number of Patients	Clinical Diagnosis†	IMF Signal for n-cadherin	IMF Signal for Plakoglobin	IMH Diagnosis	Comparison with Clinical Diagnosis
5	IVT	Normal	Normal	Not ARVC	Agree
10	ARVC	Normal	Reduced	ARVC	Agree
3	Normal	Reduced (excluded from study)	Reduced	Not possible	NA
1	Borderline for ARVC	Normal	Reduced	ARVC	NA
2	Borderline for ARVC	Normal	Normal	Not ARVC	NA
1	Sarcoidosis	Normal	Reduced	ARVC	Disagree
1	Sarcoidosis	Normal	Normal	Not ARVC	Agree
1	Dilated cardiomyopathy	Normal	Normal	Not ARVC	Agree
2	Normal	Normal	Normal	Not ARVC	Agree
1	ARVC	Normal	Normal	Not ARVC	Disagree
1	Borderline for ARVC	Reduced (excluded from study)	Reduced	Not possible	NA
1	ARVC	Reduced (excluded from study)	Reduced	Not possible	NA
1	Normal; family history of ARVC	Normal	Normal	Not ARVC	Agree

IMF=Immunofluorescent; IMH=Immunohistochemical; IVT=Idiopathic ventricular tachycardia; NA=Not applicable either because the clinical diagnosis was not definitive or because tissue samples could not be evaluated; † Clinical criteria were defined by an international ARVC task force.

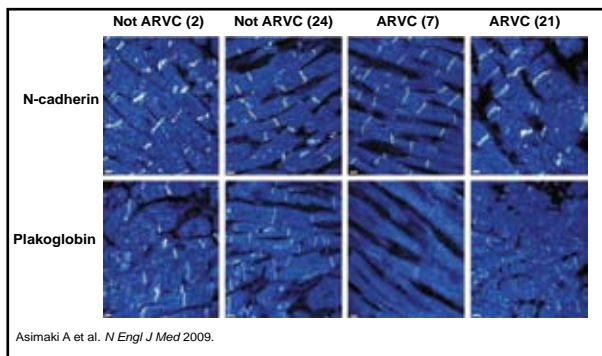
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Highlights from the



42<sup>nd</sup> Annual New York Cardiovascular Symposium

**Figure 1. Immunofluorescence Images of Endomyocardial Biopsy Samples from Two Subjects with ARVC and Two Subjects without ARVC.**



Asimaki A et al. *N Engl J Med* 2009.

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Representative images from a blinded analysis of endomyocardial biopsy samples show that immunoreactive signal levels for n-cadherin and plakoglobin in two subjects with ARVC differ from the signal levels in two subjects without ARVC. Numbers in parentheses correspond to the subject numbers in Table 1.

Patrick O’Gara, MD, Brigham & Women’s Hospital, Boston, MA,

discussed the issue of hypertrophic cardiomyopathy (HCM), which also involves genetic mutations that lead to myocyte disarray and increased collagen production (sarcomere mutations, including  $\beta$ -MHC, MBP-C, and Tn; nonsarcomere mutations, including PRKAG2, LAMP-2, and glycogen storage disease). “There is extraordinary phenotypic variability associated with hypertrophic cardiomyopathy, making it more difficult to identify and treat,” said Dr. O’Gara.

Identification of HCM and potential obstruction consists of noninvasive imaging of myocardial structure as well as left ventricular outflow gradient assessment by either provoking a response by positioning (Valsalva versus rest) in the clinical setting or performing exercise and imaging in the echocardiography lab. Outflow tract obstruction is present in 70% of patients with HCM, of which only 33% is revealed following exercise-related provocation. Identifying obstruction is clinically important, because its presence is associated with increased mortality, and such patients deserve closer clinical follow-up and consideration for more aggressive therapy [Maron M et al. *N Engl J Med* 2003]. Currently, there are no data available regarding pharmaceutical therapy and its impact on sudden cardiac death rates in these patients, Dr. O’Gara noted.

Possible *interventional* options for HCM patients include septal myectomy and alcohol septal ablation. Alcohol septal ablation involves creating an ethanol-induced myocardial infarction, while septal myectomy entails surgical removal of the hypertrophied basal septum. Myectomy has a 90% rate of success, while alcohol septal ablation has a slightly lower chance of successful outcome (70% to 80%). However, the safety of both of these interventions has been established (<2% to 3% mortality) [Nishimura R & Holmes D. *N Engl J Med* 2004; Maron BJ et al. *Circulation* 2007]. Septal myectomy is the preferred surgical intervention for HCM in the presence of concomitant problems, such as multivessel coronary disease, intrinsic mitral valve disease, midventricular obstruction, and fixed subaortic obstruction [Nishimura R & Holmes D. *N Engl J Med* 2004].

Dr. O’Gara concluded that HCM screening is important, especially for first-degree relatives. Screening should include examination, ECG, and echocardiography annually during adolescence (age 12 to 18 years) and every 3 to 5 years after age 18 years if echocardiograms are normal. When more than one family member is affected, further genetic testing may be indicated.

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