Atrial Cardiomyopathy
An Orphan Disease or Common Disorder?

Diane Fatkin, MD; Vesna Nikolova-Krstevski, PhD

Cardiac atria are intricate structures that first appear as localized ballooning of the outer curvature of the primary heart tube with subsequent chamber-specific differentiation and growth.\(^1\)\(^2\) During this process, the left and right atria acquire distinct molecular identities and specialized cell types that facilitate electric impulse generation and conduction. The right atrium contains the sinus node and the orifices of the superior and inferior caval veins and the coronary sinus. The left atrium has a larger body and smaller appendage than the right atrium, with sleeves of atrial myocardium extending into the pulmonary veins. The atria have key reservoir, conduit, and contractile functions, the perturbation of which can have disastrous consequences and result in thromboembolic stroke, heart failure, and death.

A number of factors can predispose to atrial dysfunction. The atria are exquisitely sensitive to changes in hemodynamic load, and chamber enlargement is frequently seen in conditions that impair ventricular filling or increase atrial volume such as systolic and diastolic ventricular dysfunction, valve stenosis or regurgitation, and hypertension.\(^3\) Atrial dilatation from any cause increases the propensity for tachyarrhythmias such as atrial fibrillation.\(^4\) Once arrhythmias develop, atrial contractile dysfunction or stunning can persist even with restoration of sinus rhythm after cardioversion can ensue. Atrial contractile dysfunction or stunning can persist even with restoration of sinus rhythm after cardioversion of atrial fibrillation and may result from effects of the procedure, as well as electric and structural remodeling of the atrial walls.\(^5\)\(^6\) The atria are frequently involved in diffuse cardiomyopathic processes attributable to inherited, infective, infiltrative, inflammatory, endocrine, and toxic causes. Atrial cardiomyopathy has also been recognized to occur as a primary disorder, which may manifest as disproportionate atrial dilatation, altered contractile, conduction defects, or arrhythmias.

In this issue, Disertori et al’ report a severe form of autosomal-recessive atrial cardiomyopathy observed in 13 individuals in 6 families in northeast Italy who were followed up for up to 37 years. The disease phenotype was characterized by adult-onset biatrial dilatation and progressive electric dysfunction with diminishing ECG P-wave voltages, brady-tachy syndrome, and atrial standstill. There was a high prevalence of thromboembolic complications and stroke-related death. Linkage analysis identified a disease locus on chromosome 1p36, with subsequent sequencing of candidate genes within this locus revealing a missense variant, Arg150Gln, in the natriuretic peptide precursor A gene (NPPA). All affected family members were homozygous for the Arg150Gln variant. Forty clinically unaffected family members and 16 of 192 healthy control subjects from the same geographic area were heterozygous for this variant. There were no significant differences in midregional proatrial natriuretic peptide (MR-proANP) levels between individuals carrying wild-type and those carrying heterozygous Arg150Gln alleles; however, levels were markedly decreased in individuals who were homozygous for the mutant alleles.

ANP is produced in the atria, where it is stored in its precursor form (proANP) in dense granules. In pathological conditions associated with increased atrial wall stress such as heart failure or ventricular hypertrophy, ANP is released into the circulation where it binds to guanylyl cyclase-A receptors in the kidney, adrenal gland, and vasculature, activating cGMP-dependent pathways and resulting in natriuresis, diuresis, and vasodilation.\(^8\) ANP-deficient mice exhibit hypertension, left ventricular hypertrophy, exaggerated hypertrophic responses to thoracic aortic constriction, and activation of proinflammatory cytokines.\(^9\)\(^-\)\(^11\) On the basis of these findings, it has been proposed that in addition to its antihypertensive actions, ANP acts directly on the ventricles, where it exerts an antihypertrophic effect.

Potential effects of ANP on the atria have been less well characterized, and the molecular basis for the atrial phenotype associated with the Arg150Gln variant remains to be determined. One potential explanation is that the electric and mechanical standstill associated with ANP deficiency is driven predominantly by electrophysiological defects. Low levels of ANP before and after exercise have been found previously in patients with persistent atrial standstill,\(^12\) whereas increased circulating ANP levels were found in 1 kindred with a frameshift NPPA mutation and familial atrial fibrillation.\(^13\) ANP has been shown to modulate cardiac electrophysiology in several ways, including inhibition of sympathetic nervous system activity and stimulation of parasympathetic nervous system activity. In addition, ANP has direct effects on calcium and potassium currents, as well as indirect effects on these channels by altering their autonomic regulation.\(^14\) The net effects of all these changes on heart rate and action potential duration are difficult to predict in individual cases, however,
and are influenced by basal states of neurohumoral activation, comorbidities, and drugs. Consequently, whether ANP plays any significant role in regulation of atrial electrophysiological properties in humans under normal physiological conditions has been questioned.

An alternative hypothesis is that electric defects associated with the Arg150Gln variant arise as a consequence of a structurally abnormal myocardial substrate. ANP-deficient mice have abnormal ventricular histopathology with marked ventricular fibrosis. Although this may be a consequence of ventricular hypertrophy, direct effects of ANP deficiency on extracellular matrix gene expression are possible. Atrial histopathology was not reported in these mice and was unavailable in genotyped family members. It is notable that atrial defects consistent with scar formation were seen on Carto mapping in several Arg150Gln carriers. Although atrial fibrosis may result from chronic atrial wall stretch, it seems that these changes occurred in the absence of marked atrial dilatation in some cases. ANP is a target of numerous cardiac transcription factors and plays an important role in cardiac development. In the embryonic heart, ANP is a marker of differentiating working myocardium in the atria and ventricles. After birth, levels of ANP are downregulated in the ventricle, whereas levels in the atria remain high. The effects of ANP deficiency attributable to the Arg150Gln NPPA variant on patterns of myocardial gene expression and chamber maturation will be important to determine and may reveal critical clues about the basis for atrial dysfunction in later adult life.

The findings of Disertori et al. clearly highlight the importance of elucidating the genetic basis of inherited diseases and have public health implications. The remarkable longitudinal observations indicate that atrial dilatation and electric abnormalities in homozygous Arg150Gln carriers are progressive, indicating a need for early genotyping of family members, as well as regular follow-up, thromboembolic prophylaxis, aggressive intervention to avoid hypertension, drugs and other acquired factors that might exacerbate aspects of the phenotype, and prepregnancy genetic counseling. These measures are indicated not only for family members but also for members of the local community who may prove to be heterozygous carriers. Despite its relatively high local impact, autosomal-recessive atrial dilatation with standstill is a rare and severe disorder. Less severe forms of atrial cardiomyopathy are not uncommon, however. It has been proposed that many patients with sinus node disease may have an underlying cardiomyopathy, and atrial cardiomyopathy can be a cause or a consequence of atrial fibrillation. The recognition of atrial cardiomyopathy is important because it may affect treatment choices and outcomes. For example, direct current cardioversion or pulmonary vein ablation procedures may be less successful at restoring sinus rhythm and have higher rates or recurrence of atrial fibrillation if there is an underlying myopathic substrate. The prevalence, clinical spectrum, and molecular basis of atrial cardiomyopathies are incompletely understood and are priorities for future research in this field.

Sources of Funding
The authors are supported by the National Health and Medical Research Council of Australia (grants 572772 and 1025008).

Disclosures
None.

References

KEY WORDS: Editorials • atrial cardiomyopathy • atrial natriuretic factor
Atrial Cardiomyopathy An Orphan Disease or Common Disorder?
Diane Fatkin and Vesna Nikolova-Krstevski

Circ Cardiovasc Genet. 2013;6:5-6
doi: 10.1161/CIRCGENETICS.111.000033
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue,
Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circgenetics.ahajournals.org/content/6/1/5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance
Center, not the Editorial Office. Once the online version of the published article for which permission is being
requested is located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org//subscriptions/