Hypertrophic cardiomyopathy is a common disorder that arises from mutations in genes encoding the proteins of the sarcomere. Although 9 different sarcomere genes have been implicated, point mutations in the gene encoding the β heavy chain of myosin (Myh7) or myosin binding protein C (MyBPC3) are responsible for more than half of genetically confirmed cases of HCM. Clinical management of HCM revolves around 2 significant issues: (1) reducing heart failure symptoms, if present, and (2) preventing sudden cardiac death. The underlying pathologic process in HCM is one of cellular hypertrophy that affects cardiomyocytes and is associated with myofibrillar disarray. Hypertrophy of the ventricular chambers is variable in HCM and may target the intraventricular septum leading to outflow gradient. HCM may also target the ventricular apex or hypertrophy may be concentric. Hypertrophy itself can increase the risk of sudden death by promoting subendocardial ischemia. The mechanisms that underlie the risk and incidence of sudden death in HCM are likely heterogeneous, and therefore, sudden death remains difficult to predict and manage.

In humans, HCM is variable in its presentation. The precise genetic mutation that underlies HCM offers some predictive value. For example, some mutations lead to an earlier or later onset of disease, whereas some are highly pathologic inducing a rapid onset of hypertrophy (first or second decade) or risk of highly penetrant sudden cardiac death. As a generalization, with notable exceptions, mutations in Myh7 tend to be earlier onset and more pathologic than HCM associated with MyBPC3 gene mutations. Echocardiography is a useful tool to identify HCM and can be used to identify those at risk of HCM. The availability of clinical CLIA-certified genetic testing for HCM is markedly improving the identification of at-risk individuals. The early identification of young individuals, often children, who are at risk for HCM raises the issue, what can be done to prevent the development of HCM? How can risk be reduced?

Exercise Prevents or Partially Reverses HCM

In this issue of Circulation Research, Konhilas and colleagues examined the role of exercise in preventing the development of the hypertrophic phenotype in a murine model of HCM. The model used in this study expresses a mutant myosin heavy chain impaired in its ability to bind actin, and this model develops pathology by 6 to 8 months of age. As in human HCM, this murine model displays an increase in heart weight to body weight, molecular features such as shifted myosin isoforms and ANF expression, as well as histopathologic changes including myofibrillar disarray and fibrosis. To assess the role of exercise, 2 exercise schemes were tested. In the first exercise protocol, young mice, largely prepathologic (2 months of age), were exposed to voluntary cage wheel running for 6 months. The second mode of exercise exposed older animals with established pathology (at 6 months of age) to 2 months of exercise. After exercise, mice were examined for heart weight, myocardial disarray, and fibrosis. Interestingly, most of these aspects of HCM were delayed or absent when exercise was begun early as a preventative strategy. Elements of the phenotype were reversed partially with later onset of exercise. Interestingly, fibrosis was not reversible when voluntary exercise was begun after HCM was established.

The exercise paradigm undertaken in this study was voluntary cage wheel running. This form of exercise is not enforced and therefore less likely to be associated with the adrenergic surge that other forms of exercise may have. As such, this should be considered a modest exercise program. Interestingly, exposure to the running wheel for 2 months was associated with hypertrophy in both normal control as well as genetically mutant HCM mice. Exposure to the running wheel for 6 months produced a reduction in heart weight in both control and mutant mice. Acute and chronic adaptations to exercise are known to differ, but this study emphasizes that adaptations to exercise continue to evolve over a much longer timeframe. Responses seen after 2 months of exercise may differ considerably than what is seen in chronic exercise. Further molecular characterizations of the differences seen in response to shorter and longer-term exercise are warranted.

As a more specific marker indicating the reduction of pathologic hypertrophy in HCM, Konhilas et al showed that NFAT activation was reduced by long term exercise, and this is consistent with NFAT activation as a marker of pathologic, but not physiologic, hypertrophy, as has been previously noted. Correspondingly, ANF and myosin heavy chain isoforms were shifted in response to exercise. Finally, proapoptotic markers were reduced with both exercise paradigms indicating that exercise can both prevent and partially reverse the pathology in HCM.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Departments of Medicine and Human Genetics, Institute for Cardiovascular Research, University of Chicago, Ill.

Correspondence to Elizabeth M. McNally, University of Chicago, Departments of Medicine and Human Genetics, Institute for Cardiovascular Research, 5841 S. Maryland Ave MC6088, Chicago, IL 60637. E-mail emcnally@medicine.bsd.uchicago.edu
(Circ Res. 2006;98:443-445.)
© 2006 American Heart Association, Inc.

Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/01.RES.0000214328.16941.70
Intriguingly, in this model, Akt phosphorylation differed after 2 months of exercise but not after 6 months of exercise. Akt phosphorylation in this setting may reflect 2 months of exercise rather than the onset of pathologic hypertrophy given the known role of Akt in organ growth. As with Akt, phosphorylation of GSK-3β is responsive to exercise but simultaneously influenced by the pathologic hypertrophic response in HCM. Therefore, certain signaling pathways may be differentially activated in response to both physiologic and pathologic hypertrophy.

**Diet Attenuates HCM**

Using similar models of murine HCM, Stauffer et al recently noted a significant reduction in pathologic hypertrophy in response to dietary content. In this case, a more severe HCM pathology resulted from diet based on soy products. A casein (milk) protein-based diet was associated with much less hypertrophy in male HCM mice whereas the soy-based diet promoted cardiac hypertrophy and fibrosis. Female HCM mice appeared to be less affected by diet. Because male HCM mice were more adversely affected by the soy based diet, it was reasoned that phytoestrogens, compounds readily found in soy that are known to engage estrogen receptors, mediated this physiology. It is hypothesized that female mice are more readily exposed to estrogen compounds and therefore more tolerant to the phytoestrogens present in soy. These findings underscore that variability in genetic disease may derive from environmental influences, and these findings caution against genetic determinism.

**Recommendations for HCM Patients**

Although it is tempting to speculate that modest exercise may be beneficial in human HCM patients, it should be cautioned that these environmental modifications, diet and exercise, were tested in a small animal model of HCM. Although this model is extremely informative, it remains to be determined whether these findings will translate to human HCM. One notable absence in this and other small animal models of HCM is the lack of sudden death or arrhythmia phenotype. Therefore, although modest exercise and dietary management may be effective in reducing pathologic hypertrophy, the effect on sudden death and arrhythmias in human HCM was not addressed in the present study.

Sudden death is the most devastating consequence of HCM because it may strike young, otherwise seemingly healthy individuals. Sudden death often occurs during exercise in HCM. Often, exercise associated with sudden death in HCM is characterized as “intense” or “competitive,” but it need not be. Sudden death may be the first presentation of HCM, and this leaves the clinician left to advise the survivor or family members with regard to exercise recommendations. One of the most vexing questions in the management of HCM patients is advice with regard to exercise, especially competitive exercise. In its simplest form, this question arises for the young HCM patient who wishes to participate in grade school or high school sports. Close monitoring is required during pubertal growth, and clinicians may often advise against competitive exercise and recommend modest exercise in this setting.

The more complex question arises for the competitive athlete who is incidentally noted to have significant hypertrophy on echocardiography. The competitive athlete participating in rigorous daily exercise is expected to have compensatory hypertrophy. This finding may be further complicated by the presence of syncope or near syncope that can result from a variety of causes such as dehydration, vasovagal response, or cardiac arrhythmia. For these individuals, in addition to imaging studies, family history and/or genetic testing may be helpful to confirm the diagnosis and guide recommendations.

**Acknowledgments**

E.M.M. is supported by NIH HL61322 and NIH HL78926, the Burroughs Wellcome Fund, and the Heart Research Foundation.

**References**


**Key Words:** hypertrophic cardiomyopathy | exercise | soy | casein | NFAT
Hypertrophic Cardiomyopathy: Exercise and Eat Right
Elizabeth M. McNally

doi: 10.1161/01.RES.0000214328.16941.70
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/4/443

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/