Differences in Cardiac Energetics Between Patients With Familial and Nonfamilial Hypertrophic Cardiomyopathy

To the Editor:

We have recently shown by 31P NMR spectroscopy that abnormalities in the myocardial metabolism occur in asymptomatic patients with hypertrophic cardiomyopathy (HCM). HCM is inherited in about half of the patients (familial hypertrophic cardiomyopathy, FHC). Among the most lethal genetic defects is the Arg403Gln mutation in the β-cardiac myosin heavy chain. Using a mouse model of this missense mutation, Spindler et al showed a possible link between the clinical syndrome of FHC and myocardial energetics by demonstrating decreased phosphocreatine (PCr) and increased inorganic phosphate (Pi) concentrations.

Stimulated by this report, we reanalyzed our data published in this journal1 for possible differences between FHC and patients without a known family history of HCM (nonfamilial hypertrophic cardiomyopathy, NFHC). The spectroscopic results (mean±SD) for controls (n=11, aged 27±3 years), patients with NFHC (n=8, aged 15±5 years), and patients with FHC (n=6, aged 18±10 years) were as follows: PCr/ATP: 2.46±0.53, 2.10±0.39, and 1.81±0.28 (P=0.01 versus controls); PME (phosphomonoester) • 100/PCr: 8.4±6.7, 14.1±6.2, and 18.9±15.9; Pi • 100/PCr: 9.7±7.2 (n=9), 12.3±4.5 (n=8), and 22.9±8.6 (n=5, P<0.02 versus NFHC, P<0.05 versus controls); and maximum end-diastolic interventricular septum thickness: 10±1, 23±12, and 27±11 mm. The intracellular pH was 7.08±0.03 for all groups.

These new analyses suggest that the severity of metabolic abnormalities is different in FHC and NFHC. This can be concluded from the significantly increased Pi/PCr ratio and from trends toward a greater PME/PCr and a smaller PCr/ATP ratio in FHC. Reduced PCr/ATP and increased Pi/PCr ratios may be due to increased cardiac work under resting conditions arising from the increased myocardial mass. However, FHC and NFHC showed no significant difference in the extent of hypertrophy. Alterations in energy metabolism may also occur in the absence of myocardial ischemia, as manifested in glucose metabolism. Results by others also support such a hypothesis. Moreover, in the αMHC 403/1 mouse model of FHC, the increased Pi and decreased PCr concentrations compared with wild-type mice are thought to be due to the myosin mutation and not to be a simple consequence of myocardial hypertrophy.

FHC and NFHC show striking differences in metabolite ratios. Since we have no explanation why ischemia or hypoxia should affect the FHC group while the NFHC group remains much less affected, the results from Spindler et al may also apply to our patients. In fact, the reanalyzed data provide some evidence that the changes in metabolite ratios in the myocardium of FHC patients show a relation to their inherited gene mutations. Since the 6 patients with FHC belong to 5 different families, even the retrospective determination of their genetic defects will not be sufficient. More extensive examinations of different families with several affected members will be necessary before genotype/phenotype correlations can be made.

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_Circulation_. 2000;101:e121
doi: 10.1161/01.CIR.101.12.e121

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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