Journal of the American College of Cardiology Vol. 61, No. 19, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.026

EDITORIAL COMMENT

MIBI and Mitochondria*

H. William Strauss, MD

New York, New York

In 2006, the American Heart Association Expert Consensus Panel proposed a new definition of *cardiomyopathies* (1):

> Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability.

The panelists make the point that (1):

> . . . some diseases do not have a uniformly static expression and may evolve, as a consequence of remodeling, from one category to another during their natural clinical course; eg, hypertrophic cardiomyopathy, amyloid, and other infiltrative conditions may progress from a nondilated (often hyperdynamic) state with ventricular stiffness to a dilated form with systolic dysfunction and failure.

See page 2007

Etiologies of cardiomyopathy include one or more of the following: genetics (about 20% of patients with idiopathic dilated cardiomyopathy have a relative with decreased ejection fraction), inflammation, infection, post-partum state, tachycardia, exposure to cardiotoxic agents (e.g., mediastinal radiation, chemotherapy with agents like doxorubicin or antibody therapy with trastuzumab), consumption of alcohol, and idiopathic causes (2). Regardless of etiology, injury to the myocardium impairs myocardial contractility, resulting in heart failure.

Dilated cardiomyopathy accounts for ~25% of patients with heart failure in the United States (3). Patients with dilated cardiomyopathy in heart failure have a mortality ranging from 10% to 50%/yr (4). Patients with a treatable etiology often have a good prognosis for stabilization or improvement in function. In contrast, patients without a defined etiology are at risk of progressive disease. Decreased systolic function is usually treated with medical therapy (5). In patients with left ventricular ejection fraction (LVEF) <35% or wide QRS complexes, either resynchronization therapy or an implanted cardiac defibrillator may be necessary. Despite therapy, some patients have progressive heart failure requiring a heart transplant.

A universal manifestation of cardiomyopathy is a decrease in contractile performance. Cardiac histopathology demonstrates marked alterations in the appearance of the contractile apparatus and in the appearance and location of mitochondria within the myocyte. A study of explanted hearts of patients with dilated myopathy undergoing transplantation demonstrated that "mitochondria occurred in large clusters in cytoplasm free of myofibrils, and they varied in size and shape from very small to very large. [There was a] lack of myofibrils in many cellular areas, in the center and in the periphery of a myocyte. Next to hypertrophied cells, other cells were atrophic" (6).

This appearance suggests that the mitochondria could not transfer high-energy phosphate efficiently, even if the mitochondria were working normally. As a result, assessing mitochondrial function could provide information about the performance of the heart as a muscle.

Myocardial mitochondria have the daunting task of producing about 30 kg/d of adenosine triphosphate (ATP) to maintain function (7). To meet this demand there must be continuous delivery of substrate to the mitochondria, the mitochondria must have adequate oxidative capacity, and the cell must have an effective transfer system of ATP from the mitochondria to sites of utilization (8). Based on the histopathology of the explanted hearts, it is likely that both the energy-producing and energy-transfer components of mitochondria cannot function normally in the myopathic heart.

One parameter that reflects mitochondrial function is the transmembrane potential (TMP) of the mitochondria (9). Under normal circumstances, mitochondria have the most electronegative potential of the organelles in the myocyte and therefore are the site of localization of charged lipophilic molecules that pass through the sarcolemma. Retention of these agents in the cell is proportional to TMP, and loss of TMP results in loss of the indicator. In vitro, multiple dyes can be used to determine mitochondrial function; in vivo, the choices are more limited.

The lipophilic cationic myocardial perfusion agent, technetium-99m methoxyisobutylisonitrile (MIBI) localizes primarily in mitochondria (10). The positively charged fat-soluble molecule traverses the myocardial sarcolemma, enters the cell, and localizes in the highly electronegative mitochondria. MIBI is retained in the mitochondria by the higher membrane potential. Loss of mitochondrial membrane potential results in rapid loss of MIBI from the myocyte (11,12). Investigators have tested the relationships of MIBI washout to mechanical dysfunction and prognosis.

Matsuo et al. (13) evaluated 61 patients with nonischemic congestive heart failure. The myocardial washout rate (WR), calculated from planar images, correlated with the level of B-type naturetic peptide, increased with increasing

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Section of Molecular Imaging and Therapy, Memorial Sloan Kettering Cancer Center, New York, New York. Dr. Strauss has reported that he has no relationships relevant to the contents of this paper to disclose.

New York Heart Association class and correlated negatively with LVEF. Over a mean follow-up of 12 months (range: 1 to 19 months), patients with a WR ≥28% had more events than did subjects with lower WR. Isobe et al. (14) studied 24 patients with hypertrophic myopathy. The investigators recorded planar and single-photon emission computed tomographic MIBI images following injection at rest. The heart-to-mediastinal ratio was calculated from planar images recorded at 40 min and at 4 h. The investigators found increased MIBI loss from the myocardium in patients with elevated left ventricular end-diastolic pressure and prolonged half-time of relaxation. In 17 patients with dilated cardiomyopathy (mean LVEF: 29%), Shiroodi et al. (15) measured MIBI washout and compared the results to those from 6 normal subjects (mean LVEF: 66%). The investigators acquired images at 30 min and 3.5 h after injection. Regions of interest placed in the mediastinum and the entire LV myocardium on an anterior planar view were used to determine the washout in the 3-h interval between images. Cardiomyopathy patients had a WR of 29.13 versus 14.17 for controls. WRs increased from 23.16 for patients with NYHA class I, 30.25 for class II, 32.60 for class III, and 37.5 for class IV. WR was negatively correlated with LVEF ($r^2 = 0.679$).

In this issue of the *Journal,* Hayashi et al. (16) add significant information to these observations. The investigators studied 20 patients with dilated cardiomyopathy (NYHA class I, n = 8; class II, n = 10; and class III, n = 2; mean LVEF: 33%). The myopathy patients did not have a history of coronary disease, valvular disease, hypertension, chronic atrial fibrillation, or diabetes. All myopathy subjects had cardiac catheterization with coronary angiography, dobutamine infusion to detect changes in maximum first derivative of LV pressure (LV dP/dt_{max}), endocardial biopsy (to exclude myocarditis), and reverse transcriptase–polymerase chain reaction (RT-PCR) of the biopsy specimen; 6 subjects had electron microscopy of the biopsy specimen. The electron microscopy specimens had quantitation of the number and size of mitochondria and the severity of mitochondrial degeneration.

Hayashi et al. (16) used a slightly different protocol than did Shiroodi et al. (15), recording MIBI images at 1 and 4 h after injection. Myocardial retention of MIBI was measured on planar images as: (initial net myocardial counts* − delayed net myocardial counts†)/initial net myocardial counts.

Despite minor differences in technique, the results were similar. Overall, Matsuo, Isobe, Shiroodi, and Hayashi found a decrease in myocardial MIBI retention in myopathy patients compared with those in control patients.

Hayashi divided the myopathy patients into two groups based on the WR. The group with a greater WR had a reduction in the abundance of mRNAs for mitochondrial electron transport-related enzymes on RT-PCR and more extensive mitochondrial damage on electron microscopy.

Although the number of subjects was small, the data suggest that adding a simple measurement to a myocardial perfusion scan can provide information about mitochondrial status. As stated by Ventura-Clapier et al. (8), "Despite the diversity of origin and of clinical manifestation of heart failure, defects in energy metabolism are increasingly considered as an important determinant in the progression of the disease." Hayashi et al. (16) have done an excellent job demonstrating the anatomic and functional correlation of the MIBI WR. Now it is up to the Nuclear Cardiology community to utilize this additional measurement, to define its role in patient management.

*Corrected for mediastinal background.
†Corrected for both mediastinal background and decay.

Reprint requests and correspondence: Dr. H. William Strauss, Section of Molecular Imaging and Therapy, Memorial Sloan Kettering Cancer Center, Room S113 A, 1275 York Avenue, New York, New York 10065. E-mail: harry.strauss@gmail.com.

REFERENCES

1. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies. Circulation 2006;113:1807–16.
2. Hare JA. The dilated, restrictive and infiltrative cardiomyopathies. In: Bonow RO, editor. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th edition. New York, NY: Elsevier Health Sciences Division, 2011:1561–81.
3. Hare JM. The etiologic basis of congestive heart failure. In: Colucci WS, Braunwald E, editors. Atlas of Heart Failure. 5th edition. New York, NY: Springer, 2008:29–56.
4. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424–33.
5. Liu SS, Monti J, Kargbo HM, Athar MW, Parakh K. Frontiers of therapy for patients with heart failure. Am J Med 2013;126:6–12.
6. Schaper J, Froede R, Hein S, et al. Impairment of the myocardial ultrastructure and changes of the cytoskeleton in dilated cardiomyopathy. Circulation 1991;83:504–14.
7. Murray AJ, Lindsay M, Clarke E, Clarke K. Mitochondria and heart failure. Curr Opin Clin Nutr Metab Care 2007;10:704–11.
8. Ventura-Clapier, Garnier A, Veksler V. Energy metabolism in heart failure. J Physiol 2003;555:1–13.
9. Dedkova EN, Blatter LA. Measuring mitochondrial function in intact cardiac myocytes. J Mol Cell Cardiol 2012;52:48–61.
10. Crane P, Laliberté R, Heminway S, Thoolen M, Orlandi C. Effect of mitochondrial viability and metabolism on technetium-99m-sestamibi myocardial retention. Eur J Nucl Med 1993;20:20–5.
11. Piwnica-Worms D, Kronauge JF, Chiu ML. Uptake and retention of hexakis (2-methoxyisobutyl isonitrile) technetium(I) in cultured chick myocardial cells. Mitochondrial and plasma membrane potential dependence. Circulation 1990;82:1826–38.
12. Carvalho PA, Chiu ML, Kronauge JF, et al. Subcellular distribution and analysis of technetium-99m-MIBI in isolated perfused rat hearts. J Nucl Med 1992;33:1516–21.
13. Matsuo S, Nakae I, Tsutamoto T, Okamoto N, Horie M. A novel clinical indicator using Tc-99m sestamibi for evaluating cardiac mitochondrial function in patients with cardiomyopathies. J Nucl Cardiol 2007;14:215–20.
14. Isobe S, Ohshima S, Unno K, et al. Relation of 99mTc-sestamibi washout with myocardial properties in patients with hypertrophic cardiomyopathy. J Nucl Cardiol 2010;17:1082–90.
15. Shiroodi MK, Shafiei B, Baharfard N, et al. 99mTc-MIBI washout as a complementary factor in the evaluation of idiopathic dilated cardiomyopathy (IDCM) using myocardial perfusion imaging. Int J Cardiovasc Imaging 2012;28:211–17.
16. Hayashi D, Ohshima S, Isobe S, et al. Increased ^{99}mTc-sestamibi washout reflects impaired myocardial contractile and relaxation reserve during dobutamine stress due to mitochondrial dysfunction in dilated cardiomyopathy patients. J Am Coll Cardiol 2013;61:2007–17.

Key Words: dilated cardiomyopathy ■ mitochondrial dysfunction ■ ^{99m}Tc-sestamibi scintigraphy.