Annals of Nuclear Cardiology Vol. 3 No. 1 105−109

REGIONAL SPECIFIC DISEASE AND THE ROLE OF NUCLEAR CARDIOLOGY−REVIEW ARTICLE

Energy Failure Hypothesis for Takotsubo Cardiomyopathy

Ken-ichi Hirano, MD, PhD[1)], Kentaro Shimizu, MD, PhD[2)], Yoshihiko Ikeda, MD, PhD[3)], Yoshifumi Shirakami, PhD[4)] and Hironori Nagasaka, MD, PhD[5)]

Received: December 27, 2016/Revised manuscript received: May 9, 2017/Accepted: May 16, 2017

Abstract

Takotsubo cardiomyopathy (TCM) is a transient myocardial stunning, typically showing apical ballooning. Although catecholamine toxicity, vasospasm, and disturbed microcirculation have been implicated, the precise pathophysiology of TCM is unknown. We present a two-step energy failure hypothesis which could explain the clinical course and pathogenesis. Sudden stress-induced increase in cardiac energy demand of normal subjects can be compensated for by additional supply of long chain fatty acids released from triglycerides stored in adipose tissues. Subjects at high risk for TCM cannot tolerate such stress-induced energy demand/supply imbalance, which triggers initial energy failure and induces myocytes' stunning in vulnerable mid- and apical myocardial segments. Receptor-mediated uptake for energy substrates then declines due to impairment of contraction-dependent recruitment of responsible transporters (e.g. CD36). This in turn induces the second energy failure, which prolongs the myocardial stunning. Eventually, spontaneous or therapeutic improvements in the energetics awaken the heart.

Keywords: BMIPP, Cardiac energetics, Hypothesis, Long chain fatty acid, Myocardial stunning, Takotsubo cardiomyopathy

Ann Nucl Cardiol 2017；3（1）：105−109

See page 103

Takotsubo cardiomyopathy (TCM), which was first described by Sato et al. (1, 2), is a transient severe left ventricular dysfunction, typically showing apical ballooning (3). Even though without substantial coronary obstruction, many TCM patients complain of chest pain and their electrocardiogram shows ST segment elevation, resembling myocardial infarction. Because this phenomenon is often preceded by sudden and strong mental or physical stress, it is also called stress-provoked cardiomyopathy (4) and heart failure is reportedly a common clinical complication. While most patients attain complete recovery, some suffer prolonged heart failure and the associated arrhythmias and ventricular rupture may be fatal. No single hypothesis can explain the pathophysiology, although catecholamine toxicity, vasospasm, neurogenic reaction, and disturbed microcirculation have been mentioned as involved in the pathogenesis (2−7).

Energetics is obviously important for the heart which beats 100,000 times and requires 6 kg of adenosine triphosphate (ATP) a day (8). Long-chain fatty acid (LCFA) is the major energy source for human (8, 9) and cardiomyocytes take up LCFAs by cell surface transporters such as CD36. Synthesised triglycerides (TGs) are immediately hydrolyzed by adipose triglyceride lipase (ATGL) (10) and released LCFAs are oxidised in mitochondria to produce ATPs for cardiac

doi: 10.17996/anc.17-00003

1) Ken-ichi Hirano
Laboratory of Cardiovascular Disease, Novel, Non-invasive, and Nutritional Therapeutics and Department of Cardiovascular Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan, 565-0874
E-mail: khirano@cnt-osaka.com
2) Kentaro Shimizu
Department of Traumatology and Acute Critical Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
3) Yoshihiko Ikeda
Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
4) Yoshifumi Shirakami
Department of Nuclear Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
5) Hironori Nagasaka
Department of Pediatrics, Takarazuka City Hospital, Takarazuka, Japan

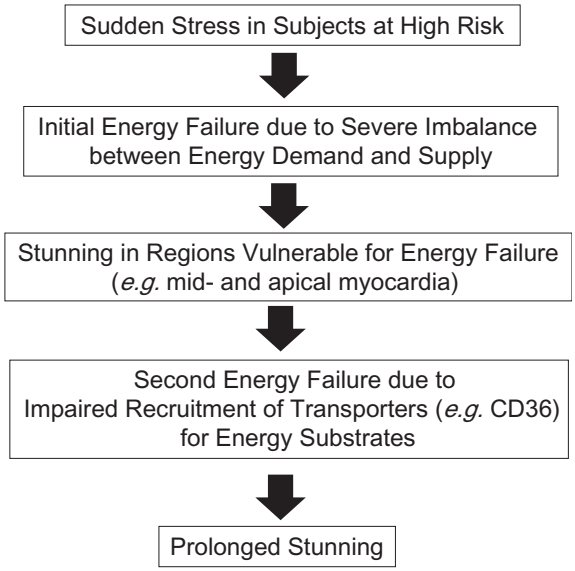

Fig. 1 A two-step energy failure hypothesis for takotsubo cardiomyopathy.

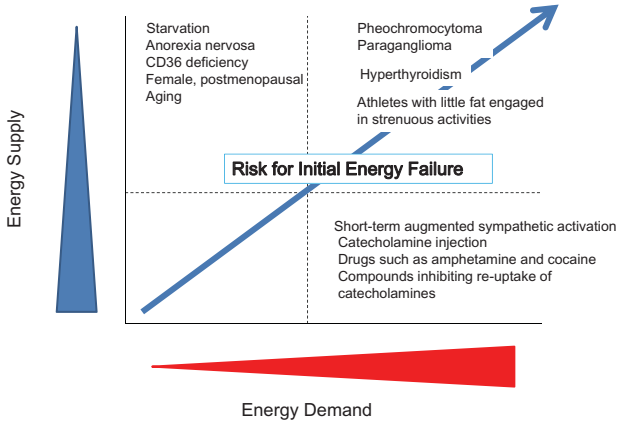

Fig. 2 Hypothetical balance between energy demand and supply for patients with takotsubo cardiomyopathy.

maximum contractility. We reported on clinical phenotypes of human genetic deficiency of CD36 and ATGL (11, 12), both of which are important molecules for cardiac energetics. CD36 deficiency presenting impaired supply of LCFAs to the heart often leads to cardiomyopathy and coronary artery diseases (11). ATGL-deficient patients suffering from severe heart failure requiring cardiac transplantation, showed a novel phenotype called TG deposit cardiomyovasculopathy (TGCV) (12, 13), characterized by massive cardiomyocyte steatosis and unique atherosclerosis with TG-deposit smooth muscle cells. In TGCV, affected cells suffer from energy failure and lipotoxiciity caused by ATGL deficiency at cellular levels (13). These clinical observations in two genetic models above strongly led us to consider that impaired energetics may be relevant for the pathogenesis of human cardiovascular diseases.

Even though having higher energy demand, the heart stores only small amounts of TGs, the deposit form of energy substrates. LCFAs derived from food are stored as TGs in adipose tissues, found in subcutaneous, visceral, pericardial, and perivascular lesions (14). When required, TGs are hydrolyzed and the released LCFAs are then delivered as energy substrates to the heart by paracrine as well as from circulation (15). Iodine-123 labeled 15-(4-iodophenyl)-3-(R, S)-methyl-iodophenyl pentadecanoic acid (^{123}I-BMIPP) (16) is a radioactive analogue for LCFA, widely used in clinics to image myocardial LCFA metabolism and diagnose patients with myocardial infarction, angina pectoris, and hypertrophic cardiomyopathy (17). In normal subjects, ^{123}I-BMIPP is rapidly accumulated into the myocardium after intravenous injection of the agent and transiently trapped in the TG pool of myocardial cells, and then metabolites of the agent are gradually washed out from the cells due to a mitochondrial β oxidation. The relatively slow kinetics of the agent compared to corresponding natural LCFAs allows visualization of the fatty acid metabolism of myocardium. The image also reflects the shift of energy utilization depending on the regional abnormalities occurred under various myocardial disorders (18, 19).

Here, our hypothesis states that energy failure triggered by severe demand/supply imbalance may lead to TCM. Furthermore, we will discuss whether our hypothesis can be integrated with previous findings, and finally how we can test our hypothesis.

Two energy failure steps involved in TCM (Fig. 1)

1. Initial energy failure due to imbalance between energy demand and supply.

Strong and unexpected stress stimulates the sympathetic nerve system and increases the heart rate and myocardial contraction, resulting in increased energy demand in the heart. It should be noted that these sympathetic stimuli simultaneously increase lipolysis in the adipose tissue, where hormone-sensitive lipase, phosphorylated by catecholamine, and other lipases hydrolyze TG to produce LCFAs (15), which are supplied to the heart. In normal subjects, the stress-induced increase in cardiac energy demand can therefore be compensated for by an increase in energy supply from adipose tissues.

A hypothetical balance between energy supply and demand in TCM patients, described in previous reports, is illustrated in Fig. 2. Patients with anorexia nervosa (20) or malnutrition (21) suffer from a deficient supply of energy substrates such as LCFA and glucose due to the loss of adipose tissue and starvation. Postmenopausal women and elderly people appear to have sufficient adipose tissue, but their adipocytes generate less lipolysis and are resistant to sympathetic stimuli (22). Subjects with genetic CD36 deficiency have defective uptake of LCFA (9, 23). Subjects using drugs and compounds which

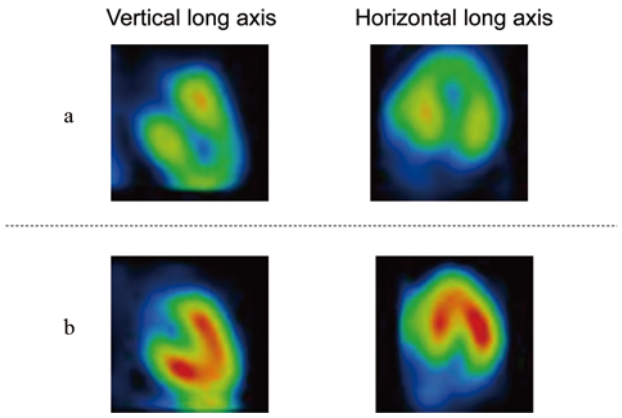

Fig. 3 Representative images for BMIPP scintigraphy in a patient with TCM.

A 56-year-old female with anorexia nervosa was transferred to our emergency center due to sudden collapse, then diagnosed as TCM. Upper and lower panels are images of BMIPP scintigraphy at the acute and recovery phases of TCM, respectively.

a: BMIPP scintigraphy on hospital day 5 showed a defect in the region of the apex. **b**: On hospital day 33, the defect had disappeared.

increase sympathetic activities are at high risk of a surge in energy demand. Patients with pheochromocytoma, paraganglioma (24), hyperthyroidism, and athletes with little body fat and engaged in strenuous activities are at the highest risk due to increased demand for and reduced supply of energy. Because these subjects cannot tolerate sudden stress, initial energy failure can be triggered.

We also need to mention about circumstances and situations at the onset of TCM. Disasters and critical medical conditions such as earthquake and subarachnoid hemorrhage affect food intake and appetite. Subjects with stress may be obligated to be fasting and away from foods mentally as well as physically. This nutritional disadvantage may increase the risk for initial energy failure.

2. Second energy failure due to akinesis/non-contraction-induced impaired uptake of energy substrates

Energy substrates for heart are taken up by cell surface transporters and receptors. CD36 is one of major transporters responsible for taking up LCFAs (9). Many previous papers described that, in TCM patients, the uptake of BMIPP was defective in the akinetic myocardium and that BMIPP is useful for the diagnosis for TCM (25-28). During the recovery phase of TCM, however, these uptakes can become normalized, as shown in Fig. 3. Furthermore, even in *in vitro* biological experiments using rodents' cardiomyocytes, cell surface and membrane translocation of CD36 was found to be contraction-dependent (29). If this finding applies to human transporters *in vivo*, TCM-associated stunning in the myocardium can be expected to impair the translocation of the transporter for energy substrates to the cell surface. This would then trigger the second energy failure, which prolongs myocardial stunning.

3. The recovery phase

During the second energy failure, affected cardiomyocytes survive using alternate and low-energy substrates such as amino acids or ketone bodies, and subsequent spontaneous or therapeutic improvement in energetics awakens the myocytes. Once they start contracting, these myocytes recruit the transporters for LCFA and glucose to the cell surface to regain their major energy source for maximum contractility.

Takotsubo shape and energy failure

1. Possibility of segmental difference of myocardial workload and energy demand

The myocardial fibers in the left ventricle, which consist of three layers, contract/relax and rotate and twist the ventricle, providing the substantial mechanical power required for systole/diastole. Previous cinefluorographic studies demonstrated that mid- and apical segments were more hyperkinetic than the basal one. In addition, recent studies including 2-dimensional speckle tracking demonstrated that the mid- and apical myocardium may be subject to higher longitudinal strains than the basal one (30). It has also been reported that apical ventricular segments have higher concentrations of adreno-receptors (4). Therefore, it is tempting to speculate that cardiomyocytes in the mid- and apical region feature a higher physiological workload and more energy demand than those in the basal region, although the energetics at the single cardiomyocyte level needs clarification. We therefore consider the mid- and apical myocardium to be more susceptible to initial energy failure than the basal one.

2. Epicardial adipose tissue (EAT) as emergent energy source for the heart

The mid- and apical myocardia are usually overlapped anatomically with EAT, whereas the basal one are not. Previous *in vitro* study mentioned that EAT may be a local energy source for the heart (31). We think that EAT may function as an emergent and supplementary source for delivering LCFA to the adjacent myocardium with higher energy demand at the time of sudden and massive stress. While EAT has much lower volume than subcutaneous and visceral fat, it is much closer to the heart which may be advantageous for delivering energy source, especially during collapse due to disaster and stress. Under pathological conditions resulting in less EAT, such as starvation and emaciation, myocardium overlapped with EAT may be more susceptible to energy failure. In this connection, rodent models for TCM (32) have no EAT or certainly less than human.

The ampulla shape is common, but not observed in all TCM cases (7, 33), which may be explained by possible individual differences in segmental susceptibility to energy failure and the distribution and volume of EAT.

Relationship with previous findings and other hypotheses

1. Catecholamine cardiotoxicity

Many papers have reported enhanced catecholamine levels in TCM patients (3, 4). We believe that catecholamine surge is an important condition for initial energy failure and could explain some pathological findings such as contraction band necrosis and interstitial edema (4). As long as the balance between energy demand and supply is maintained, catecholamine alone cannot account for the development of TCM.

2. Epicardial coronary vasospasm and impaired microcirculation

In studies including the initial case series (1), some TCM patients exhibited epicardial coronary vasospasm (4-7). In addition, impaired coronary microcirculation and microvascular constriction (34-36) have been proposed as a possible underlying mechanism for TCM. In these hypotheses, irrespective of epicardial artery or microvasculature, vasoconstriction or spasms associated with increased catecholamines are believed to be involved in the pathogenesis of TCM. It is particularly of importance to know possible relationship between impaired microcirculation or microvascular constriction and energy failure hypotheses. It is noted that some patients with TGCV, which is a model for energy failure as described above, suffer from vasospastic angina (37, 38). Experimental and clinical studies for vascular or microvascular energetics, of which information is currently scarce, are important issues for near future.

To test hypothesis

Myocardial energetics in TCM patients could be tested with magnetic resonance spectrometry, but this technique has not been widely used. It may be worth testing in subsequent clinical trials whether administration (*e.g.* intracoronary) of an alternative energy source can relieve symptoms and shorten the recovery phase for TCM patients. We believe that cardiomyovascular energetics can be important for understanding as yet unexplained, unknown, or undefined cardiovascular diseases.

Contributors

KH raised the concept of hypothesis and wrote the manuscript. KS, YI, YS, and HN contributed to the construction of hypothesis based upon their specialties.

Acknowledgments

We would like to mention that, because of the limitation of space, we did not cite references for each case report and series in Fig. 2. The authors would like to thank Drs. Hitonobu Tomoike, Yoshihiro Tochino, and Shinsuke Nanto for critical comments and discussions. The authors would like to thank Mr. Jan K. Visscher for proofreading the manuscript.

Sources of funding

None.

Conflicts of interest

We declare that we have no conflicts of interest.

Reprint requests and correspondence:
Ken-ichi Hirano, MD, PhD
Laboratory of Cardiovascular Disease, Novel, Non-invasive, and Nutritional Therapeutics (CNT), Graduate School of Medicine, Osaka University, 6-2-3, Furuedai, Suita, Osaka, Japan
E-mail: khirano@cnt-osaka.com

References

1. Sato H, Tateishi H, Uchida T. Takotsubo type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, editors. Clinical aspect of myocardial injury: from ischemia to heart failure. Tokyo, Japan. Kagaku Hyoronsha 1990: 56-64.
2. Lüscher TF. Takotsubo: a Japanese contribution to cardiology. Eur Heart J 2016; 37: 2803-5.
3. Wittstein IS. Apical-ballooning syndrome. Lancet 2007; 370: 545-7.
4. Nef HM, Möllmann H, Akashi YJ, et al. Mechanisms of stress (takotsubo) cardiomyopathy. Nat Rev Cardiol 2010; 7: 187-93.
5. Kurisu S, Kihara Y. Tako-tsubo cardiomyopathy: clinical presentation and underlying mechanism. J Cardiol 2012; 60: 429-37.
6. Yoshinaga K, Tomiyama Y, Sakakibara M, et al. Relatively high prevalence of Takotsubo cardiomyopathy (stress-induced cardiomyopathy) in the Japanese population－contribution of cardiac imaging in the identification of takotsubo cardiomyopathy and its differentiation from acute coronary syndrome. Curr Cardiovasc Imaging Rep 2015; 11: 1-8.
7. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. N Engl J Med 2015; 373: 929-38.
8. Neubauer S. The failing heart－an engine out of fuel. N Engl J Med 2007; 356: 1140-51.
9. Tanaka T, Okamoto F, Sohmiya K, et al. Lack of myocardial iodine-123 15-(p-iodiphenyl)-3-R, S-methylpentadecanoic acid (BMIPP) uptake and CD36 abnormality－CD36 deficiency and hypertrophic cardiomyopathy. Jpn Circ J 1997; 61: 724-5.
10. Haemmerle G, Lass A, Zimmermann R, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. Science 2006; 312: 734-7.
11. Hirano K, Kuwasako T, Nakagawa-Toyama Y, et al. Pathophysiology of human genetic CD36 deficiency. Trends Cardiovasc Med 2003; 13: 136-41.
12. Hirano K, Ikeda Y, Zaima N, et al. Triglyceride deposit cardiomyovasculopathy. N Engl J Med 2008; 359: 2396-8.
13. Hirano K, Tanaka T, Ikeda Y, et al. Genetic mutations in adipose triglyceride lipase and myocardial up-regulation of

peroxisome proliferated activated receptor-γ in patients with triglyceride deposit cardiomyovasculopathy. Biochem Biophys Res Commun 2014; 443: 574-9.
14. Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. Am J Physiol Endocrinol Metab 2012; 303: E937-49.
15. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. Prog Lipid Res 2009; 48: 275-97.
16. Goodman MM, Kirsch G, Knapp FF Jr. Synthesis and evaluation of radioiodinated terminal p-iodophenyl-substituted alpha- and beta-methyl-branched fatty acids. J Med Chem 1984; 27: 390-7.
17. Kurata C, Tawarahara K, Taguchi T, et al. Myocardial emission computed tomography with iodine-123-labeled beta-methyl-branched fatty acid in patients with hypertrophic cardiomyopathy. J Nucl Med 1992; 33: 6-13.
18. Tamaki N, Yoshinaga K. Novel iodinated tracers, MIBG and BMIPP, for nuclear cardiology. J Nucl Cardiol 2011; 18: 135-43.
19. Knapp FF Jr, Kropp J, Franken PR, et al. Pharmacokinetics of radioiodinated fatty acid myocardial imaging agents in animal models and human studies. Q J Nucl Med 1996; 40: 252-69.
20. Rotondi F, Manganelli F, Lanzillo T, et al. Tako-tsubo cardiomyopathy complicated by recurrent torsade de pointes in a patient with anorexia nervosa. Intern Med 2010; 49: 1133-7.
21. Shimizu K, Ogura H, Wasa M, et al. Refractory hypoglycemia and subsequent cardiogenic shock in starvation and refeeding: report of three cases. Nutrition 2014; 30: 1090-2.
22. Rebuffé-Scrive M, Eldh J, Hafström LO, et al. Metabolism of mammary, abdominal, and femoral adipocytes in women before and after menopause. Metabolism 1986; 35: 792-7.
23. Kushiro T, Saito F, Kusama J, et al. Takotsubo-shaped cardiomyopathy with type I CD36 deficiency. Heart Vessels 2005; 20: 123-5.
24. Van Spall HG, Roberts JD, Sawka AM, et al. Not a broken heart. Lancet 2007; 370: 628.
25. Moriya M, Mori H, Suzuki N, et al. Six-month follow-up of takotsubo cardiomyopathy with I-123-beta-metyl-iodophenyl pentadecanoic acid and I-123-meta-iodobenzyl-guanidine myocardial scintigraphy. Intern Med 2002; 41: 829-33.
26. Kurisu S, Inoue I, Kawagoe T, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. J Am Coll Cardiol 2003; 41: 743-8.
27. Ito K, Sugihara H, Kinoshita N, et al. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using ^{99m}Tc-tetrofosmin, ^{123}I-BMIPP, ^{123}I-MIBG and ^{99m}Tc-PYP myocardial SPECT. Ann Nucl Med 2005; 19: 435-45.
28. Matsuo S, Nakajima K, Kinuya S, et al. Diagnostic utility of ^{123}I-BMIPP imaging in patients with Takotsubo cardiomyopathy. J Cardiol 2014; 64: 49-56.
29. Koonen DP, Glatz JF, Bonen A, et al. Long-chain fatty acid uptake and FAT/CD36 translocation in heart and skeletal muscle. Biochim Biophys Acta 2005; 1736: 163-80.
30. Takigiku K, Takeuchi M, Izumi C, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. Circ J 2012; 76: 2623-32.
31. Marchington JM, Pond CM. Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. Int J Obes 1990; 14: 1013-22.
32. Ueyama T, Kasamatsu K, Hano T, et al. Emotional stress induces transient left ventricular hypocontraction in the rat via activation of cardiac adrenoceptors: a possible animal model of‘tako-tsubo’cardiomyopathy. Circ J 2002; 66: 712-3.
33. Kawai S, Kitabatake A, Tomoike H; Takotsubo Cardiomyopathy Group. Guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. Circ J 2007; 71: 990-2.
34. Nishikawa S, Ito K, Adachi Y, et al. Ampulla (‘takotsubo’) cardiomyopathy of both ventricles: evaluation of microcirculation disturbance using ^{99m}Tc-tetrofosmin myocardial single photon emission computed tomography and doppler guide wire. Circ J 2004; 68: 1076-80.
35. Kume T, Akasaka T, Kawamoto T, et al. Assessment of coronary microcirculation in patients with takotsubo-like left ventricular dysfunction. Circ J 2005; 69: 934-9.
36. Lüscher TF, Templin C. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. Eur Heart J 2016; 37: 2816-20.
37. Kaneko K, Kuroda H, Izumi R, et al. A novel mutation in PNPLA2 causes neutral lipid storage disease with myopathy and triglyceride deposit cardiomyovasculopathy: a case report and literature review. Neuromuscl Disord 2014; 24: 634-41.
38. Ando S, Usui M, Matsumoto T, et al. Vasospastic angina in patients with systemic triglyceride storage disease with Jordans’ anomaly and cardiomyopathy. Jpn Circ J 1996; 60: 124-9.