

Inhibition of fatty acid oxidation as an approach to treat diastolic heart failure

John R. Ussher¹ and Jagdip S. Jaswal²

¹Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Canada;

²Cardiovascular Research Centre, Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada

Correspondence: Dr. John Ussher, Lunenfeld-Tanenbaum Research Institute, 5-1001-DD, 25 Orde Street, Toronto, Ontario, Canada M5T 3H7
Tel: +1 (416) 586 4800 ext. 2308, fax: +1 (416) 586 5186, e-mail: ussher@lunenfeld.ca

Abstract

Heart failure (HF) is characterized by an impaired ability of the ventricle to fill with and eject blood commensurate with the metabolic demands and requirements of the body, and has emerged as a major cause of morbidity and mortality in the developed world. It is now becoming clear that a significant portion of the world's HF population does not exhibit defects in systolic function, but rather presents with significant declines in diastolic function. Unfortunately, there are no approved therapies for the management/treatment of diastolic HF, with current therapies aimed at improving patient symptoms. Recent evidence illustrates that similar to systolic HF, a number of metabolic abnormalities in the myocardium appear to be associated with the progression of diastolic dysfunction/HF. As ventricular relaxation during diastole is an energy-consuming process dependent on ATP hydrolysis, the optimization of cardiac energetics, potentially through inhibiting myocardial fatty acid oxidation rates, may represent a novel target for improving diastolic function. ■ Heart Metab; 2013;61:20–24

Keywords: Cardiac energetics; diastolic heart failure; diastolic dysfunction; fatty acid oxidation.

Introduction

Cardiovascular disease is currently a primary cause of death and disability. With recent advances in evidence-based medicine, the overall management of patients with cardiovascular diseases has greatly improved, although there has been a concomitant rise in the prevalence of heart failure (HF). HF is not a disease, but rather a complex clinical syndrome, defined by an impaired ability of the ventricle to fill with (diastolic HF) and/or eject (systolic HF) blood corresponding to the metabolic demands and requirements of the body [1]. HF has emerged as a leading cause of morbidity and mortality in the developed world. The etiology of HF

is generally attributed to pre-existing ischemic heart disease, but it can also be of nonischemic/idiopathic origin. Epidemiological studies have identified that approximately 50–60% of HF patients have a dilated left ventricular chamber and reduced ejection fraction (systolic HF), while the remainder have a normal left ventricular chamber, and preserved ejection fraction (diastolic HF) [2, 3]. As such, systolic HF and diastolic HF are often considered to be two separate entities that contribute to clinically recognized HF. While there are a number of approved therapies for the management of systolic HF, there are currently no approved therapies for those with diastolic HF, with treatment

Abbreviations

Ang II: angiotensin II; **CoA:** coenzyme A; **CPT:** carnitine palmitoyl-transferase; **GLUT:** glucose transporter; **HF:** heart failure; **PDH:** pyruvate dehydrogenase; **PET:** positron emission tomography; **SR:** sarcoplasmic reticulum; **TDGA:** 2-tetradecylglycidic acid

primarily aimed at improving patient symptoms. However, recent work has demonstrated that targeting cardiac energetics, in particular reducing myocardial fatty acid oxidation rates, may be a novel approach to treat diastolic HF. Whereas we have previously described the characteristics that differentiate diastolic from systolic HF [3], the aims of this article are to describe the etiology of diastolic HF, the metabolic aspects of ventricular relaxation that contribute to diastolic function, the alterations in cardiac metabolism that accompany the development of diastolic HF, and the potential for optimizing myocardial energetics as an approach to treating diastolic HF.

Etiology and characteristics of diastolic HF

Although ejection fraction is preserved, diastolic HF is characterized by the classic symptoms of HF in addition to abnormalities of diastolic function. In particular, an increase in ventricular chamber stiffness/decreased distensibility impairs ventricular relaxation and thus filling at normal diastolic pressures. Interestingly, approximately half of all HF patients have preserved ejection fraction. As such, the prevalence of diastolic HF is similar to that of HF in general [2]. Predominant risk factors predisposing to the development of diastolic HF include increasing age, hypertension, obesity, dyslipidemia, diabetes and gender (ie, female sex) [4, 5]. At the gross morphological level, hallmark alterations in left ventricular structure and geometry (ie, left ventricular remodeling) also characterize diastolic HF. Concentric left ventricular hypertrophy, exemplified by increased left ventricular wall thickness, increased left ventricular mass, and an increase in the mass to cavity ratio, is a prominent change observed in diastolic HF [6]. The increase in left ventricular wall thickness also contributes to decreased ventricular compliance/increased stiffness. Alterations in the expression of titin isoforms (ie, decreased titin 2A expression) and increased fibrosis further decrease ventricular compliance in the setting of diastolic HF, and contribute to impaired ventricular relaxation [7].

Despite differences in etiology and left ventricular remodeling, diastolic HF is treated with many of the same therapeutic agents as systolic HF. Current therapeutic strategies focus on resolving the symptoms of diastolic HF by means of optimal blood pressure and heart rate control [8]. However, there is limited evidence from randomized clinical trials demonstrating that these therapies possess equivalent efficacies with respect to decreasing morbidity and mortality in the setting of diastolic HF relative to systolic HF. As such, there exists a need to identify novel therapeutic interventions to decrease the burden of diastolic HF. Of interest, one of the consequences of increased left ventricular wall thickness may provide such a novel target. Although the increase in left ventricular wall thickness may initially serve a compensatory function by normalizing wall stress in the presence of chronic pressure overload (ie hypertension) that can predispose to diastolic HF, the change does become maladaptive, and correlates with increased myocardial oxygen consumption [9]. As cardiac muscle predominantly relies on oxidative metabolism to meet its energetic requirements, optimizing energy substrate metabolism such that ATP is generated in an oxygen-efficient manner (ie by inhibiting fatty acid oxidation/stimulating glucose oxidation) may represent a novel strategy that may have therapeutic utility in the treatment of diastolic HF (see below).

Active ventricular relaxation and diastolic function

Ventricular diastole is the period during which the ventricles relax and fill with blood. Blood flow into the ventricle is governed by two key phases, first an early (E) diastolic phase arises due to the flow of blood from the atria down its pressure gradient into the ventricle, while the second phase occurs later as a result of atrial contraction (A). Therefore, the E/A ratio is often used as a diagnostic measure, because it is reduced during diastolic dysfunction as a greater fraction of the left ventricular end diastolic volume becomes dependent on the A phase.

Ventricular relaxation itself is the process by which the myocardium returns to its original length and tension, and takes place once the aortic valve closes and the mitral valve is still closed. Furthermore, it is an energy-consuming process as ATP hydrolysis is required for myosin detachment from actin filaments, Ca²⁺ dissociation from troponin C, and sarcoplasmic reticulum (SR) Ca²⁺ reuptake (*Figure 1*) [3]. Optimal

ATP supply and tight regulation of the metabolic pathways that generate ATP is thus essential for the maintenance of normal diastolic function. Support for this concept is provided by demonstrations that diastolic function is impaired in pathologies including pressure overload hypertrophy (secondary to systo-

mic hypertension), obesity, and diabetes, all of which can significantly impact myocardial metabolism [10, 11]. Whether myocardial metabolism can be targeted to improve diastolic HF will be discussed below.

Cardiac glucose oxidation

Glucose and lactate are the primary carbohydrates metabolized by the heart (for an in-depth review of the regulation of cardiac carbohydrate oxidation, please refer to Jaswal et al [10]). Glucose transporters (ie, GLUT-1/4) are responsible for glucose uptake into the cardiac myocyte whereby glucose catabolism for ATP production can be separated into two major components: glycolysis and glucose oxidation. Glycolysis generates pyruvate and accounts for less than 10% of the total ATP produced by the aerobic adult heart [12]. If glycolysis is coupled to glucose oxidation, the pyruvate generated from glycolysis will be converted into acetyl coenzyme A (CoA) by the enzymatic action of pyruvate dehydrogenase (PDH).

Cardiac fatty acid oxidation

Before oxidation in cardiac mitochondria, fatty acids must first be activated into fatty acyl CoA by fatty acyl CoA synthase, which converts a fatty acid into a fatty acyl CoA moiety in an ATP-dependent manner (for an in-depth review of the regulation of cardiac fatty acid oxidation, please refer to Lopaschuk et al [11]). Mitochondrial uptake of fatty acyl CoA requires a complex of proteins that relies on a carnitine-dependent shuttle system [13]. Carnitine palmitoyl-transferase I (CPT-I), which is the rate-limiting enzyme for mitochondrial fatty acid uptake and subsequent oxidation converts fatty acyl CoA esters into their respective fatty acylcarnitine moieties [14, 15]. The acylcarnitine is subsequently transported into the mitochondrial matrix by carnitine translocase, and converted back into its respective fatty acyl CoA moiety by CPT-II [11]. Fatty acyl CoA esters are sequentially oxidized inside the mitochondrial matrix by the successive enzymatic activities of acyl CoA dehydrogenase, enoyl CoA hydratase, 3-L-hydroxyacyl CoA dehydrogenase, and 3-ketoacyl CoA thiolase. Fatty acid β -oxidation progressively shortens fatty acyl CoA esters by two carbon units via the liberation of acetyl CoA, while also generating reducing equivalents (NADH and reduced flavine adenine dinucleotide), which act as electron donors for the electron transport chain, in order to drive ATP synthesis by the process of oxidative phosphorylation [16].

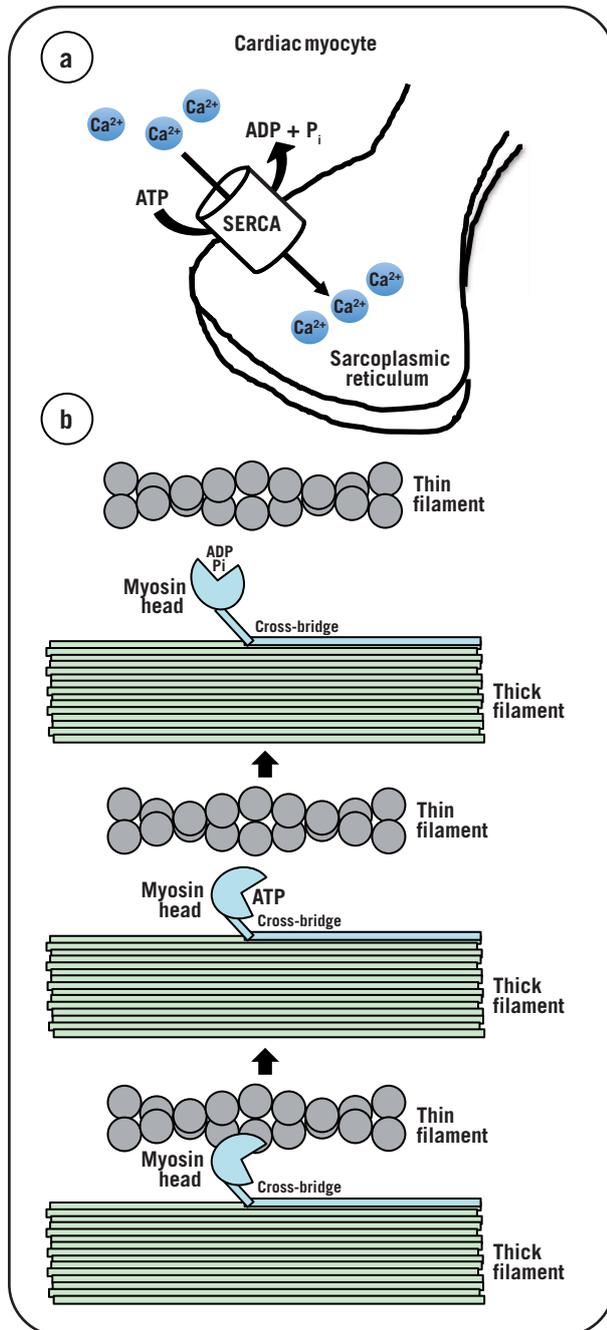


Fig. 1 ATP-dependency of ventricular relaxation. Ventricular relaxation is an energy-consuming process, with ATP hydrolysis essential for (a) sarco/endoplasmic reticulum Ca²⁺-ATPase reuptake into the SR, and during the process of (b) cross-bridge cycling (once power stroke induces the sliding of myofilaments, ATP binds to the myosin head releasing it from actin, which is followed by ATP hydrolysis, allowing the cross-bridge to return to its original orientation in the resting state). SR, sarcoplasmic reticulum

Glucose–fatty acid cycle

In its simplest form, the glucose–fatty acid cycle refers to the inverse relationship between glucose and fatty acid oxidation, whereby increases in the oxidation of one energy substrate (ie, fatty acids) decrease the oxidation of the competing substrate (ie, glucose), a phenomenon originally described by the work of Dr Philip Randle and colleagues in the 1960s [17]. In addition to being the more oxygen-efficient fuel, increasing glucose oxidation also improves efficiency by reducing the amount of ATP required to remove excess protons arising from the hydrolysis of glycolytically derived ATP uncoupled from the subsequent mitochondrial oxidation of pyruvate (ie, glucose oxidation) [18]. Therefore, one could postulate that by inhibiting fatty acid oxidation rates in the heart, the corresponding increase in glucose oxidation would conserve ATP and possibly improve left ventricular relaxation in diastolic HF.

Energy metabolism in diastolic HF

It is now becoming clear that similar to systolic HF, diastolic HF is also accompanied by significant changes in cardiac energy metabolism. In type 1 diabetic Akita mice, diastolic function is selectively impaired, and is associated with increased myocardial fatty acid oxidation rates, which coincides with a substantial accumulation of intramyocardial ceramide and diacylglycerol levels [19]. Such a metabolic signature has been shown to negatively impact cardiac function and cardiac insulin sensitivity [10, 20]. Of interest is the fact that these metabolic abnormalities and diastolic dysfunction were reversed following insulin therapy [19], suggesting that energy metabolism represents a potential target to alleviate diastolic dysfunction/HF. Type 2 diabetes-associated diastolic dysfunction in Zucker diabetic fatty rats demonstrated similar metabolic derangements, as an assessment of myocardial metabolism by positron emission tomography (PET) revealed elevations in myocardial fatty acid oxidation rates and reduced myocardial glucose uptake [21]. Patients with nonischemic diastolic dysfunction present with a similar metabolic profile, as PET imaging studies demonstrated elevations in both myocardial fatty acid uptake and oxidation, while myocardial glucose uptake was reduced [22]. Furthermore, recent studies utilizing either a 2-week angiotensin II (Ang II) or phenylephrine infusion in mice to induce diastolic dysfunction demonstrate that both models selectively reduce myocardial glucose oxidation rates due to an inhibition of

PDH activity [23]. Intriguingly, treatment with the Ang II type 1 receptor blocker, irbesartan, improved diastolic function and was associated with a restoration of myocardial PDH activity and subsequent glucose oxidation rates [23]. Collectively, these findings suggest that the metabolic alterations associated with diastolic dysfunction/HF may contribute to disease pathology.

Inhibition of fatty acid oxidation to improve diastolic function in diastolic HF

In striking contrast to the overall premise of this article, studies performed in the 1990s demonstrated that inhibition of CPT-1 with 2-tetradecylglycidic acid (TDGA) induces left ventricular hypertrophy and diastolic dysfunction [24, 25]. However, neither of these studies actually measured the effect of TDGA treatment on myocardial fatty acid oxidation rates. On the contrary, treatment with the fatty acid oxidation inhibitor, trimetazidine, prevents the increase in diastolic $[Ca^{2+}]_i$ and the decrease in SR Ca^{2+} content in rats subjected to acute myocardial injury following a 2-day isoprenaline administration [26]. These improvements in diastolic Ca^{2+} handling may account for the improvements in diastolic function observed in type 2 diabetic *db/db* mice treated with trimetazidine [27]. Ranolazine, a US Food and Drug Administration approved agent for treating angina pectoris by inhibition of the late inward sodium current, has also been shown to inhibit fatty acid oxidation at similar concentrations [10], and has been reported to improve diastolic function in deoxycorticosterone acetate salt-induced hypertensive mice, as well as in humans [28, 29]. Furthermore, weight loss as a result of gastric bypass surgery reduced myocardial oxygen consumption and fatty acid oxidation rates, which was associated with a 28% improvement in left ventricular relaxation [30]. Finally, reducing fatty acid oxidation rates by inhibition of CPT-1 with perhexiline corrects diastolic dysfunction and improves exercise capacity in patients with hypertrophic cardiomyopathy [31]. Despite these promising findings, the exact role myocardial fatty acid metabolism plays in contributing to diastolic function and its potential contribution towards the overall pathology of diastolic dysfunction/HF is a relatively understudied area deserving of further attention.

Conclusions

As there are currently no approved therapies for the treatment of diastolic HF, there is a growing need to

improve our understanding of the physiology/pathophysiology of diastolic function/dysfunction. As ventricular relaxation is an active, energy-requiring process, and recent studies have demonstrated alterations in cardiac energy metabolism in the setting of diastolic dysfunction/HF, the optimization of cardiac energetics may represent a novel therapeutic approach to improve this condition. However, whether this can be achieved by inhibiting fatty acid oxidation in the heart remains to be determined. ■

Acknowledgment: Dr. Ussher is a fellow of Alberta Innovates-Health Solutions and the Canadian Institutes of Health Research.

REFERENCES

- Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS et al (2001) ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 104:2996–3007
- Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A et al (2012) Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 355:260–269
- Jaswal JS, Ussher JR (2012) Differentiating diastolic dysfunction from classic heart failure. *Heart and Metabolism* 57:4–7
- Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG et al (2002) Obesity and the risk of heart failure. *N Engl J Med* 347:305–313
- Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D (2009) Relations of lipid concentrations to heart failure incidence: the Framingham Heart Study. *Circulation* 120:2345–2351
- Gaasch WH, Zile MR (2011) Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol* 58:1733–1740
- Wood P, Piran S, Liu PP (2011) Diastolic heart failure: progress, treatment challenges, and prevention. *Can J Cardiol* 27:302–310
- Meyer T, Shih J, Aurigemma G (2013) Heart failure with preserved ejection fraction (diastolic dysfunction). *Ann Intern Med* 2013;158:ITC5-1–ITC5-15; quiz ITC5-16
- Devereux RB, Roman MJ, Palmieri V, Okin PM, Boman K, Gerds E et al (2000) Left ventricular wall stresses and wall stress-mass-heart rate products in hypertensive patients with electrocardiographic left ventricular hypertrophy: the LIFE study. *Losartan Intervention For Endpoint reduction in hypertension. J Hypertens* 18:1129–1138
- Jaswal JS, Keung W, Wang W, Ussher JR, Lopaschuk GD (2011) Targeting fatty acid and carbohydrate oxidation – a novel therapeutic intervention in the ischemic and failing heart. *Biochim Biophys Acta* 1813:1333–1350
- Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC (2010) Myocardial fatty acid metabolism in health and disease. *Physiol Rev* 90:207–258
- Ussher JR, Lopaschuk GD (2006) Clinical implications of energetic problems in cardiovascular disease. *Heart and Metabolism* 32:9–17
- Murthy MS, Pande SV (1984) Mechanism of carnitine acylcarnitine translocase-catalyzed import of acylcarnitines into mitochondria. *J Biol Chem* 259:9082–9089
- Murthy MS, Pande SV (1987) Some differences in the properties of carnitine palmitoyltransferase activities of the mitochondrial outer and inner membranes. *Biochem J* 248:727–733
- Murthy MS, Pande SV (1987) Malonyl-CoA binding site and the overt carnitine palmitoyltransferase activity reside on the opposite sides of the outer mitochondrial membrane. *Proc Natl Acad Sci U S A* 84:378–382
- Ussher JR, Jaswal JS, Lopaschuk GD (2012) Pyridine nucleotide regulation of cardiac intermediary metabolism. *Circ Res* 111:628–641
- Randle PJ, Garland PB, Hales CN, Newsholme EA (1963) The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1:785–789
- Jaswal JS, Ussher JR, Lopaschuk GD (2009) Myocardial fatty acid utilization as a determinant of cardiac efficiency and function. *Clin Lipidol* 4:379–389
- Basu R, Oudit GY, Wang X, Zhang L, Ussher JR, Lopaschuk GD, Kassiri Z (2009) Type 1 diabetic cardiomyopathy in the Akita (Ins2WT/C96Y) mouse model is characterized by lipotoxicity and diastolic dysfunction with preserved systolic function. *Am J Physiol Heart Circ Physiol* 297:H2096–2108
- Zhang L, Ussher JR, Oka T, Cadete VJ, Wagg C, Lopaschuk GD (2011) Cardiac diacylglycerol accumulation in high fat-fed mice is associated with impaired insulin-stimulated glucose oxidation. *Cardiovasc Res* 89:148–156
- van den Brom CE, Huisman MC, Vlasblom R, Boontje NM, Duijst S, Lubberink M et al (2009) Altered myocardial substrate metabolism is associated with myocardial dysfunction in early diabetic cardiomyopathy in rats: studies using positron emission tomography. *Cardiovasc Diabetol* 8:39
- Rijzewijk LJ, van der Meer RW, Lamb HJ, de Jong HW, Lubberink M, Romijn JA et al (2009) Altered myocardial substrate metabolism and decreased diastolic function in nonischemic human diabetic cardiomyopathy: studies with cardiac positron emission tomography and magnetic resonance imaging. *J Am Coll Cardiol* 54:1524–1532
- Mori J, Basu R, McLean BA, Das SK, Zhang L, Patel VB et al (2012) Agonist-induced hypertrophy and diastolic dysfunction are associated with selective reduction in glucose oxidation: a metabolic contribution to heart failure with normal ejection fraction. *Circ Heart Fail* 5:493–503
- Wolkowicz PE, Urthaler F, Forrest C, Shen H, Durand J, Wei CC et al (1999) 2-Tetradecylglycidic acid, an inhibitor of carnitine palmitoyltransferase-1, induces myocardial hypertrophy via the AT1 receptor. *J Mol Cell Cardiol* 31:1405–1412
- Litwin SE, Raya TE, Gay RG, Bedotto JB, Bahl JJ, Anderson PG et al (1990) Chronic inhibition of fatty acid oxidation: new model of diastolic dysfunction. *Am J Physiol* 258:H51–56
- Meng D, Feng L, Chen XJ, Yang D, Zhang JN (2006) Trimetazidine improved Ca²⁺ handling in isoprenaline-mediated myocardial injury of rats. *Exp Physiol* 91:591–601
- Li YJ, Wang PH, Chen C, Zou MH, Wang DW (2010) Improvement of mechanical heart function by trimetazidine in db/db mice. *Acta Pharmacol Sin* 31:560–569
- Lovelock JD, Monasky MM, Jeong EM, Lardin HA, Liu H, Patel BG et al (2012) Ranolazine improves cardiac diastolic dysfunction through modulation of myofilament calcium sensitivity. *Circ Res* 110:841–850
- Hayashida W, van Eyll C, Rousseau MF, Pouleur H (1994) Effects of ranolazine on left ventricular regional diastolic function in patients with ischemic heart disease. *Cardiovasc Drugs Ther* 8:741–747
- Peterson LR, Saeed IM, McGill JB, Herrero P, Schechtman KB, Gunawardena R et al (2012) Sex and type 2 diabetes: obesity-independent effects on left ventricular substrate metabolism and relaxation in humans. *Obesity (Silver Spring)* 20:802–810
- Abozguia K, Elliott P, McKenna W, Phan TT, Nallur-Shivu G, Ahmed I et al (2010) Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. *Circulation* 122:1562–1569