Chapter 3

Contractile Reserve in Dilated Cardiomyopathy

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http://dx.doi.org/10.5772/55413

1. Introduction

Dilated cardiomyopathy (DCM) is one of the most common types of cardiomyopathy worldwide. It is characterized by progressive chamber dilatation and myocardial systolic dysfunction and diagnosed by finding left ventricular (LV) enlargement and impaired systolic LV function (LV ejection fraction less than 50% or fractional shortening of less than 25-30%). Angiotensin-converting enzyme inhibitors and ß-blockers are the best and popular therapeutic interventions for DCM that promotes amelioration of systolic LV dysfunction among 20-45% DCM patients [1 - 5]; nonetheless, the 5-year mortality rate of DCM remains 10-35% under these medical therapy [6 - 8].

The predictive assessment of LV function is clinically important in medical management of DCM, particularly when considering the indication for heart transplantation. In most patients with heart failure, symptoms are not present at rest but become limiting with exercise. Nevertheless, the major measures for LV function of DCM, such as echocardiography, are generally performed under the static condition. In addition, LV contractile function at rest is not reliable for an assessment of the reversibility of LV contraction, that is contractile reserve [3, 4]. Therefore, it is important to evaluate LV functional response under dynamic conditions by use of pharmacological as well as exercise stress [9].

This article reviews the current status of myocardial contractile reserve with our findings, including procedures for evaluating contractile reserve, clinical implications, and molecular biological significance.

2. Contractile reserve in DCM

2.1. Myocardial contractile reserve

Myocardial contractile reserve measured by stress testing has been defined as a difference LV function at rest and under load. To date, the assessment of myocardial contractile reserve limitedly applied to evaluate the myocardial viability exclusively in patients with LV dysfunction and coronary artery disease. Nowadays, glowing evidences suggest the clinical importance to evaluating the contractile reserve in non-ischemic DCM [9, 10]. In particular to the case of DCM, the assessment of myocardial contractile reserve is mainly focused to evaluate the presence of residual LV contractile reserve.

2.2. Pathophysiological implications

Determinant factors of myocardial contractile reserve include the Frank-Starling mechanism, the force-frequency effect, and adrenergic stimulation [11, 12]. In DCM patients, myocardial contractile reserve to adrenergic stimulation is impaired [9].

Myocardial contractile reserve by stress testing provide important prognostic information in DCM [13]. Previous studies reported that patients exhibiting load-induced enhancement of systolic LV function had better clinical outcomes [10, 14 - 17] and LV contractile reserve is a useful marker to predict future LV functional improvement in the treatment of beta blocker or after cardiac resynchrnonization therapy [18 - 21].

In addition, myocardial contractile reserve is associated with other prognostic biomarkers and molecule expressions in cardiomyocyte. Firstly, LV inotropic reserve is associated with exercise capacity [14]. The contractile reserve correlates with peak oxygen consumption (peak VO_2) in cardiopulmonary exercise testing [22, 23]. Moreover, patients with greater increase in myocardial contractile reserve achieved a greater peak VO_2 [23]. Secondly, impaired LV contractile reserve was reported to be associated with cardiac sympathetic dysfunction measured by myocardial iodine-123-metaiodobenzylgluanidine (^{123}I-MIBG) scintigraphy [24]. Finally, we reported that reduced adrenergic myocardial contractile reserve related to myocardial expression of contractile regulatory protein mRNAs, such as beta$_1$-adrenergic receptor, sarcoplasmic reticulum Ca^{2+}-adrenergic triphosphatase, and phospholamban [25].

Moreover, the assessment of LV response using a stress testing may also help in the screening or monitoring the presence of latent myocardial dysfunction in patients with the initial phase of cardiomyopathy overt normal resting echocardiographic parameters who had exposure to cardiotoxic agents [26].

3. How to evaluate contractile reserve?

Myocardial contractile reserve is usually defined as a difference between LV function at rest and under load. LV function has been evaluated by a variety of modalities, such as echocar-

diography, cardiac pool scintigraphy, and cardiac catheterization. Exercise and inotropic stress have been used as stress protocols for the assessment of contractile reserve. Both stresses provoke a generalized increase of regional wall motion with an increment of ejection fraction [27]. Although regional LV wall dysfunction is commonly caused by coronary artery ischemia, regional wall motion abnormality is sometimes shown in non-ischemic cardiomyopathy [28].

The selection of evaluation method and stress modality mainly depends on the patient's exercise capacity, the purpose of the examination, and medical contraindications.

3.1. Exercise stress

Exercise stress is a very useful and the best physiological stressor. Therefore, exercise testing should be performed in patients who are physically allowed [27]. Images can be obtained by use of pre- and within one minute of post- treadmill, upright or supine cycle exercise. However, the weakness of stress echocardiography is that it depends on image quality and its use by the occasional user may be attached with loss of accuracy.

3.2. Dobutamine stress

Pharmacologic stress testing is preferred for patients unable to exercise. Use of low dose dobutamine seems to be the best stress method for the assessment of myocardial contractile reserve, unless there is a contraindication [29]. The protocol of dobutamine infusions vary from investigators, but the patient usually undergo the stress testing using standardised incremental infusions of 5, 10, and 20 μg/kg/min [30]. The safety dose has been documented as high as 40 μg/kg/min and serious complications occurs in about 0.3 %.

3.3. Interpretension

In stress echocardiography, global LV function at rest is assessed by calculation of ejection fraction or wall motion score index on the resting images. After collecting stress images, both data are compared for the development of global function. As for the evaluation of regional function, regional wall motion scoring is generally used. Generally, the critical level to define the presence of contractile reserve is defined as an increase of more than 5% in the global LV ejection fraction [31].

Some studies have evaluated the adrenergic contractile reserve by measurement of increase in the maximal first derivative of LV pressure (LV dP/dt_{max}) using a cardiac catheter in patients with non-ischemic LV dysfunction [15, 32].

3.4. Stress testing protocol in our studies

Our protocol for the evaluation of myocardial contractile reserve consists of low-dose dobutamine infusion and cardiac catheterization (Figure 1). Although a lot of investigations which reported dobutamine stress testing were measured by echocardiography, we more accurately evaluate LV response using catheterization with a high-fidelity micromanometer.

Initially, routine diagnostic left and right heart catheterization are performed. A 6-F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter, CD Leycom, Zoetermeer, The Netherlands) is placed in the LV cavity for measurement of LV pressure. We evaluate LV dP/dt_{max} as an index of LV contractility [33]. After collection of baseline hemodynamic data, dobutamine is infused intravenously at incremental doses of 5, 10, and 15 μg/kg/min and hemodynamic measurements are made at the end of each 5-minute infusion period. In addition, we calculate ΔLV dP/dt_{max} as an index of myocardial contractile reserve [25]. ΔLV dP/dt_{max} is defined as the percentage increase in LV dP/dt_{max} induced by dobutamine, and this index is defined on the basis of the formula.

$$\Delta LV\ dP/dt_{max}(x) = [LV\ dP/dt_{max}(x) - LV\ dP/dt_{max}(baseline)] / LV\ dP/dt_{max}(baseline)$$

where x = the dose of dobutamine (μg/kg/min)

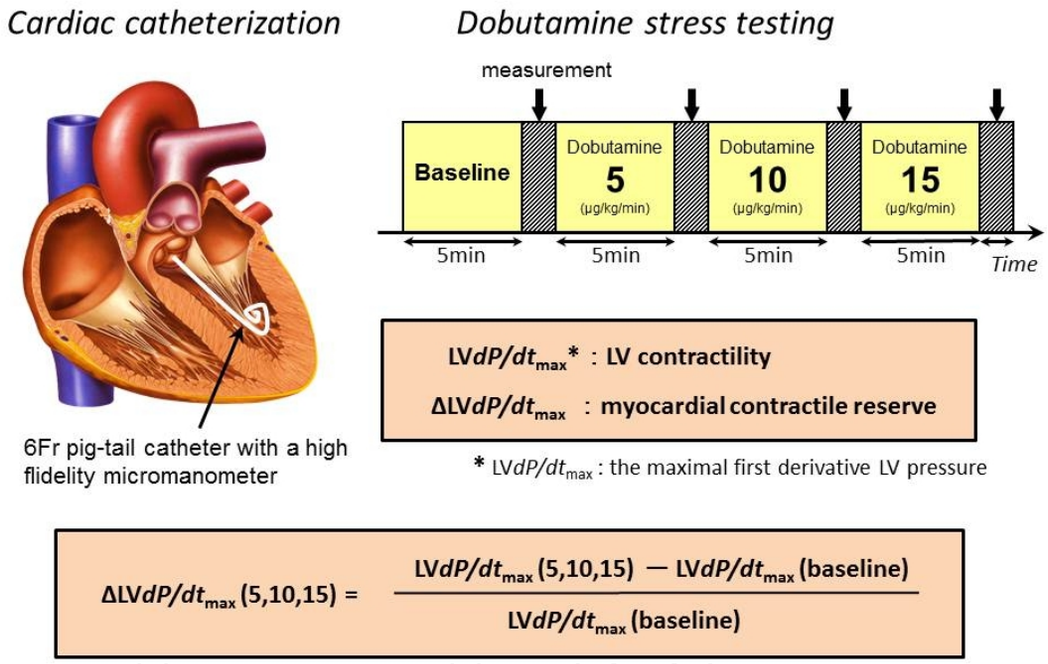


Figure 1. Protocol for evaluating myocardial contractile reserve in DCM

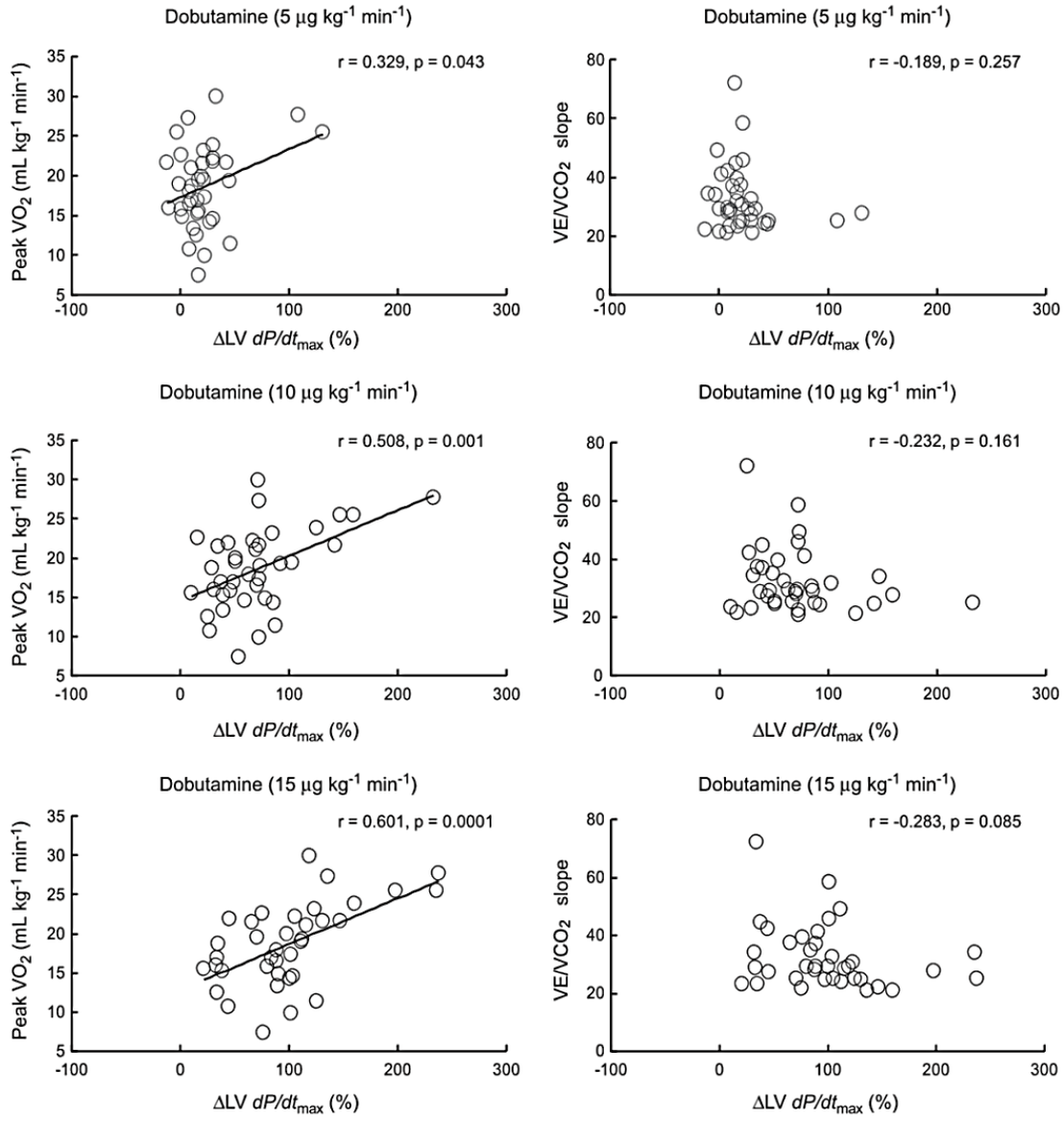
4. Clinical implications of myocardial contractile reserve

4.1. Exercise capacity and contractile reserve

The presence of LV inotropic response during dobutamine stress testing is associated with a better performance [14]. Patients with markedly reduced myocardial contractility at rest, but with good residual contractile reserve, have a favorable exercise capacity. On the other hand, patients with mildly abnormal myocardial contractility at rest, but reduced contractile reserve have a poor capacity [34].

http://dx.doi.org/10.5772/55413

Recently, we reported the association between myocardial contractile reserve and exercise capacity in 38 idiopathic DCM patients [23]. Peak VO_2 was significantly correlated with ΔLV dP/dt_{max}, but not with LV dP/dt_{max} at baseline. In addition, the correlation became more pronounced as the dose of dobutamine was increased (Figure 2). Multivariate regression analysis revealed that ΔLV dP/dt_{max} was independently correlated with peak VO_2 (p=0.011). There was no correlation between minute ventilation/carbon dioxide production (VE/VCO_2) slope and ΔLV dP/dt_{max}.



ΔLV dP/dt_{max} was significantly correlated with peak VO_2, and the correlation became more pronounced as the dose of dobutamine was increased. In contrast, no significant inverse correlation between ΔLV dP/dt_{max} and VE/VCO_2 slope was apparent, even at the maximum dose of dobutamine. ΔLV dP/dt_{max} is the percentage increase in LV dP/dt_{max} induced by dobutamine. [23]

Figure 2. Correlation between myocardial contractile reserve and peak VO_2, VE/VCO_2 slope.

Paraskevaidis, et al. reported the utility of evaluating the presence of myocardial contractile reserve in patients with intermediate values of peak VO_2 (10-14 mL/kg/min) [35]. They concluded that contractile reserve may yield the greatest incremental prognostic value in gray zone candidates for cardiac transplantation and provide further information for the risk stratification.

These results suggested that myocardial contractile reserve can be used as an adjunct or an alternative to predict peak VO_2 in patients with heart failure, especially when the patients fall into the gray zone of peak VO_2 or when the patients have a difficulty in ambulation.

4.2. Cardiac sympathetic function and contractile reserve

In 2005, we reported the correlation of impaired contractile reserve with cardiac sympathetic dysfunction in 24 DCM patients [24]. A significant correlation was observed between the delayed ^{123}I-MIBG heart-mediastinum ratio (HMR) and the percentage change in LV dP/dt_{max} from the baseline to the peak heart rate (Figure 3). The delayed ^{123}I-MIBG HMR was significantly lower in patients with a worsening change in LV dP/dt_{max} ($p=0.004$). As for the expression of mRNA, there is no significant difference in abundance for sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2). However, SERCA2/glyceraldehyde-3-phosphate dehydrogenase (GAPDH) ratio was significantly lower in low HMR group, indicating that reduced expression of SERCA2 is associated with impaired cardiac sympathetic activity.

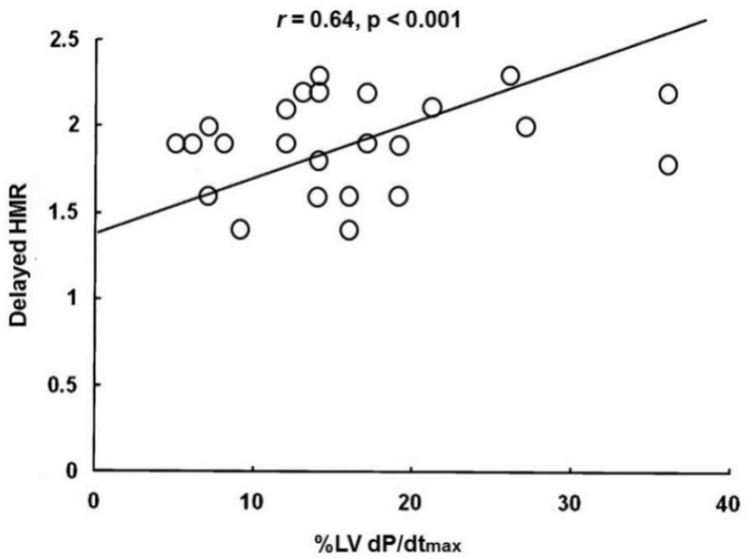


Figure 3. Relationship between the delayed ^{123}I-MIBG HMR and the percentage change in LV dP/dt_{max} from the baseline to the peak or critical heart rate. (modified from [24])

This result indicated that the myocardial ^{123}I-MIBG scintigraphy may reflect myocardial contractile reserve, and may be useful in non-invasively predicting residual contractile reserve.

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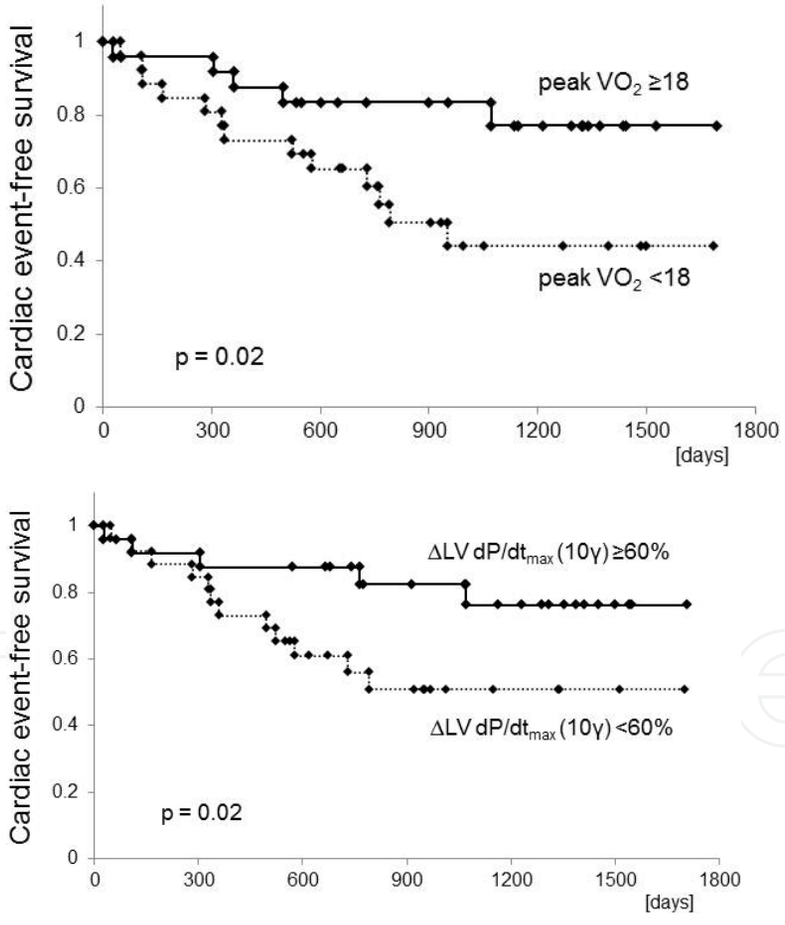
4.3. Prognosis and contractile reserve

LV contractility has been considered to be the most powerful predictor of prognosis in DCM. Around 2000, an array of studies reported the association between LV contractile reserve and prognosis, and the presence of contractile reserve came to be considered as the most powerful prognostic predictor [10, 14 - 17].

We investigated the contractile reserve during dobutamine infusion in relation to the prognosis in 52 patients with mildly symptomatic DCM. In the ΔLV $dP/dt_{max}(10)$ <60% group, cardiac events were significantly higher than in the ΔLV $dP/dt_{max}(10)$ ≥60% group. Peak VO_2 <18 (mL/kg/min) (HR:3.18, p=0.029) and ΔLV $dP/dt_{max}(10)$ <60% (HR:3.25, p=0.026) were comparable predictors of cardiac events (Figure 4). This result indicated that evaluating the myocardial contractile reserve in dobutamine stress testing and peak VO_2 in cardiopulmonary exercise testing may be complementary approaches to predict a prognosis of non-ischemic DCM.



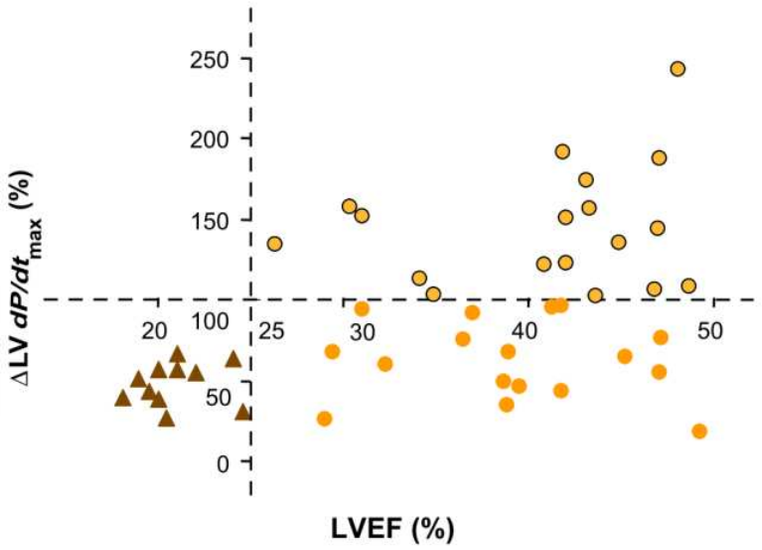
In the peak VO_2 <18 (mL/kg/min) group, cardiac events were significantly higher than in the peak VO_2 ≥18 group. In addition, cardiac events were significantly higher in the ΔLV $dP/dt_{max}(10)$ <60% group than in the ΔLV $dP/dt_{max}(10)$ ≥60% group. Peak VO_2 <18 (HR:3.18, p=0.029) and ΔLV $dP/dt_{max}(10)$ <60% (HR:3.25, p=0.026) were comparable predictors of cardiac events.

Figure 4. Kaplan-Meier analysis of cardiac event-free survival in 52 DCM patients.

Kasama S, et al. evaluated the LV response using dobutamine gated blood pool scintigraphy in 22 DCM patients [20]. In the good response group to 15 μg/kg/min dobutamine (the presence of contractile reserve; echocardiographic LV ejection fraction >5% improvement), LV systolic function was significantly improved after 1 year of ß-blocker therapy. Cardiac sympathetic nerve activity and New York Heart Association functional class also improved with cardiac reverse remodeling. In addition, they investigated contractile reserve using ^{99m}Tc-tetrofosmin quantitative gated single photon emission computed tomography (SPECT) and the similar findings were shown [21].

4.4. Molecular biological significance and contractile reserve

Recently, we reported that dobutamine stress testing is a useful diagnostic tool for evaluating adrenergic myocardial contractile reserve. This residual contractile reserve is related to alterd myocardial expression of $ß_1$-adrenergic receptor, SERCA2a, and phospholamban genes in DCM [25]. In this study, 46 asymptomatic or mildly-symptomatic DCM patients were enrolled and classified into 3 groups based on baseline LV ejection fraction and ΔLV dP/dt_{max} (Figure 5). The amounts of $ß_1$-adrenergic receptor, SERCA2a, and phospholamban mRNA were significantly smaller in group IIa and IIb than in group I (Table 1). This result indicated that impaired contractile reserve by dobutamine stress testing may be associated with molecular remodeling caused by the overactivation of sympathetic nerve system.



Patients were classified into 3 groups: group I (orange with black circles), ΔLV dP/dt_{max} >100% (LV ejection fraction [LVEF] >25%); group IIa (orange circles), ΔLV dP/dt_{max} ≤100% and LVEF >25%; and group IIb (brown triangles), ΔLV dP/dt_{max} ≤100% and LVEF ≤25%. [25]

Figure 5. Relation between baseline LV ejection fraction and LV dP/dt_{max}

mRNA	Group I	Group IIa	Group IIb
$Beta_1$-AR	1.39 ± 0.68	0.71 ± 0.19*	0.66 ± 0.29*
$Beta_2$-AR	1.29 ± 0.92	0.95 ± 0.18	0.91 ± 0.40
GRK2	1.54 ± 0.63	1.53 ± 0.26	1.59 ± 0.58
G_5 alpha	1.18 ± 0.40	0.94 ± 0.17	1.04 ± 0.34
G_{i2} alpha	0.78 ± 0.35	0.77 ± 0.15	0.85 ± 0.25
SERCA2a	0.60 ± 0.29	0.36 ± 0.08*	0.37 ± 0.12*
Phospholamban	0.82 ± 0.28	0.56 ± 0.12*	0.36 ± 0.16*
Ryanodine receptor-2	0.74 ± 0.42	0.56 ± 0.17	0.69 ± 0.23
Calsequestrin	1.34 ± 0.58	1.16 ± 0.25	1.30 ± 0.44
Na^+/Ca^{2+} exchanger	1.69 ± 0.76	1.14 ± 0.14	1.46 ± 0.84
Data are means ± SD. *p <0.05 vs. group I. AR = adrenergic receptor; GRK2 = G protein-coupled receptor kinase 2; mRNA = messenger ribonucleic acid; SERCA2a = sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase 2a.			

Data are means ± SD. * p<0.05 vs. group I.

AR= adrenergic receptor, GRK2+ G protein-coupled receptor kinase 2; mRNA = messenger ribonucleic acid; SERCA 2a = sarcoplasmic reticulum Ca^{2+} adenosine triphosphate 2a.

Table 1. Relative Abundance of Contractile Regulatory Protein mRNAs in Endomyocardial Biopsy Specimens Relative to the Corresponding Amount of Glyceraldehyde-3-Phosphate Dehydrogenase mRNA [25]

4.5. Latest findings about contractile reserve

At present, it is reported that the patients with non-ischemic DCM have an impairment of coronary microcirculation and their coronary flow reserve is diminished [36, 37]. Skalidis EI, et al. investigated the association between LV contractile reserve and coronary flow reserve [38]. They studied 14 patients with idiopathic DCM and 11 control subjects. A significant correlation between coronary flow reserve and the corresponding contractile reserve in the vascular territory was reported. Interstingly, Otasevic P, et al. reported the relation of myocardial histomorphometric features in endomyocardial biopsy specimens and LV contractile reserve assessed by dobutamine stress echocardiography [39]. It was revealed that myocyte diameter and interstitial fibrosis strongly correlated with change in the wall motion score index, followed by the change in LV ejection fraction. Recently, Yamada S, et al. invetigated the association between myocardial blood volume and LV contractile reserve in 21 DCM patients using myocardial contrast echocardiography [40]. Myocardial blood volume was not correlated with any parameters of resting LV function, but significantly correlated with percent increase in LV ejection fraction during dobutamine stress testing. They speculated in their paper that myocardial histomorphometric features in DCM conceivably cause the reduction in myocardial blood volume, being related to the depressed contractile reserve.

5. Conclusions and future perspectives

As present, stress testing, especially by dobutamine infusion, is considered to be useful for detecting residual contractile reserve in DCM. Myocardial contractile reserve is usually detected by echocardiography, but sometimes evaluated by other modalities for accuracy, such as quantitative gated SPECT, cardiac pool scintigraphy, and LV pressure analysis. A lot of previous studies revealed that the presence of residual contractile reserve is associated with a good prognosis and impaired contractile reserve is affected by multiple factors including, but not limited to, exercise intolerance, cardiac sympathetic dysfunction, reduced myocardial blood flow and histopathological changes. In addition, the possibility is suggested that myocardial contractile reserve would predict a reversibility of LV dysfunction after initiation of cardioprotective therapy. Evaluating residual contractile reserve may have key information to predict response to interventional therapy. Therefore, further studies are required in order to detect non-responders with no available future reverse remodeling.

Acknowledgements

The authors express gratitude to Yasuko Kureishi Bando and Takahisa Kondo for careful reading of the manuscript. We would also like to thank the patients who participated in our researches.

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