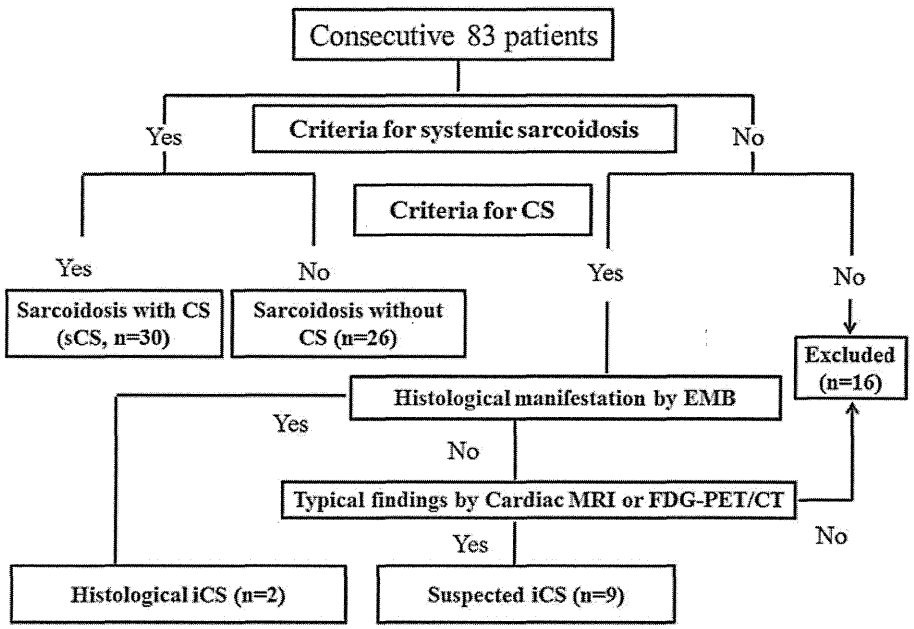

Fig. 1. Classification of the enrolled cases. All 83 patients were classified with the use of criteria for both systemic sarcoidosis and cardiac sarcoidosis (CS). EMB, endomyocardial biopsy; MRI, magnetic resonance imaging; FDG-PET/CT, ^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography; iCS, isolated CS.

of a segmented inversion-recovery gradient-echo sequence. Delayed enhancement images were obtained 3–10 minutes after the intravenous infusion of a gadolinium-chelate contrast material (meglumine gadopentetate, 0.15 mmol/kg) with the use of a cardiac-gated T1-weighted pulse sequence. The inversion times were typically 220–320 ms. At the Cardiovascular Imaging Clinic, images were acquired during repeated breath-holds with the use of a 1.5-T scanner (Philips Achieva) with a phased-array coil and steady-state free precession. Standard delayed enhancement images were acquired 10 minutes after contrast administration (meglumine gadopentetate, 0.2 mmol/kg) with the use of a segmented inversion-recovery gradient-echo sequence. The inversion delay times were typically 220–300 ms.

On cardiac MRI, the typical findings of CS on cine imaging were defined as limited focal dyskinesis, thinning basal septal wall, or aneurysm. Additionally, unexplained LGE was defined as a possible finding of CS. Cases with chronic kidney disease (creatinine clearance rate <30 mL/min) were assessed by myocardial edema and scarring on T2-weighted-imaging black blood (T2WI-BB).

FDG-PET/CT Studies

FDG-PET/CT scans were performed with the use of an Aquiduo machine (Toshiba Medical, Tokyo, Japan). The CT data were obtained in 2-mm slices with a 15° helical pitch at 120 kV and 50–100 mA, with a matrix of 512 × 512 pixels. Patients fasted for >12 hours, and oral hydration and bladder emptying were completed before CT data collection. CT data for attenuation correction and anatomic coregistration were obtained during expiratory breath-holding without contrast media administration. After CT scanning, the patients received an intravenous injection of 3.7 MBq/kg FDG and underwent whole-body scans 60 minutes later. The PET data were obtained in 3-dimensional mode for 2 minutes in each bed position. The PET data consisted of a matrix of 128 × 128 pixels.

Visual Qualitative and Semiquantitative Analyses of FDG-PET/CT Images

Data obtained from FDG-PET/CT were analyzed by 2 nuclear medicine radiologists blinded to the clinical data, who assessed FDG uptake in the myocardium. Myocardial FDG uptake in CS was defined as a "focal" or "focal on diffuse" pattern.[15] For quantitative analysis, the myocardial mean standardized uptake value (SUV) was measured in each of the 17 lesions in accordance with American Heart Association guidelines.[19] We used the coefficient of variance (CV) of the mean SUV.[20] Moreover, we assessed the utility of the ratio of the highest mean SUV to the lowest mean SUV as a more convenient marker. Thirty-one healthy men, matched for age and sex, were enrolled as control subjects.

Therapeutic Effect and Long-Term Prognosis

Ejection fraction, left ventricular diastolic dimension according to echocardiography, and serum B-type natriuretic peptide (BNP) level were compared before and after therapy in sCS and iCS patients. To assess the improvement in BNP level after prescribing prednisolone, we calculated ΔBNP (%) as (BNP level before prednisolone administration − BNP level after prednisolone administration)/BNP level before prednisolone administration.

To assess outcome with the use of the event-free curve, the primary end points were defined as admission for heart failure and all-cause mortality. The data were compared in terms of the use of prednisolone and left ventricular dysfunction (defined as ejection fraction $<50\%$).

Statistical Analysis

Categoric data are presented as n (%) and continuous data as mean ± SD. We performed Kruskal-Wallis 1-way analysis of variance for comparison among ≥3 groups. The nonparametric test of Mann-Whitney-Wilcoxon with Holm correction was used to

compare 2 groups. Ninety-five percent confidence intervals (CIs) were calculated, and P values of $<.05$ were considered to be statistically significant. The area under the receiver operating characteristic (ROC) curve (AUC) was calculated. The optimal cutoff values were considered as those closest to the point of 100% sensitivity and 100% specificity, according to the standard method. The sensitivity, specificity, positive predictive value, and negative predictive value were determined by the relevant cutoff values. ROC curves were compared with the use of Medcalc version 13.1.0.0 software (Medcalc Software, Ostend, Belgium). The statistical difference in Kaplan-Meier curves was assessed by means of the log rank test. Statistical analysis was performed with the use of SPSS version 11.0.1 J software (SPSS, Chicago, Illinois).

Results

The classification of the 83 cases is shown in Fig. 1. The number of cases that fulfilled the major and minor criteria did not differ between the sCS and iCS groups. iCS was associated with a high rate of limited thinning of the interventricular septum, similar to that noted in sCS patients. No significant differences were observed in complete atrioventricular block, gallium uptake, left ventricular dysfunction, ventricular tachycardia, focal dyskinesis, or diffuse hypokinesis between the sCS and iCS groups. However, the prevalence of ventricular aneurysm was higher in iCS cases than in sCS cases ($P = .046$). The ejection fraction in iCS cases was lower than that in sCS cases ($P = .025$; Table 2).

Amiodarone prescription and implantable cardioverter-defibrillator application were more prevalent in iCS than in sCS cases (Table 3). The use of other therapies, including corticosteroids, was not significantly different between the groups.

Details of the 11 iCS cases that were diagnosed based on histologic and clinical findings are presented in Table 4. The absence of ischemic heart disease was confirmed in all 11 iCS patients, and all 9 suspected iCS cases underwent cardiac MRI or FDG-PET/CT.

Overall, 12 cases (4 sCS, 5 iCS, and 3 sarcoidosis without CS) underwent endomyocardial biopsy. Sarcoidosis was not identified in the myocardium of any sCS cases. Among all CS cases (n = 9), noncaseating granulomas were present in only 2 iCS patients (22.2%).

Cardiac MRI

Cardiac MRI data were obtained from 24 cases (10 sCS, 5 iCS, and 9 sarcoidosis without CS; Fig. 2). LGE examination was performed in 22 cases; the remaining 2 cases were assessed with the use of T2WI-BB.

All CS cases presented positive LGE findings. Among the 9 cases of sarcoidosis without CS, 6 had positive LGE findings. Assessment of transmurality on LGE examination demonstrated that fibrosis was frequently present in the epicardium (68.4% of cases). In particular, LGE was more frequently observed in the epicardial wall in sCS and iCS cases compared with other transmural patterns (76.9% vs 35.9%; $P = .011$). The transmurality of LGE was not statistically different between sCS and iCS cases (Fig. 3, left).

The localization of LGE is presented in Fig. 3 (right). The most frequent site was the basal anteroseptal wall (68% of cases). The septal lesions in sCS and iCS cases had a significantly higher rate of LGE compared with the other lesions (52.9% vs 19.1%; $P < .001$); their localization was not statistically different between iCS and sCS.

Among the iCS cases, 3 patients exhibited interventricular septum thinning, and an aneurysm was observed in the other 2. In particular, 1 iCS case—diagnosed based on histologic manifestations—exhibited an aneurysm on LGE examination. T2WI-BB examination revealed myocardial edema and scar lesions in 1 sCS case and 1 iCS case.

FDG-PET/CT

FDG-PET/CT data were obtained from 62 cases, including 19 sCS cases, 7 iCS cases (all cases were suspected iCS), 5 cases of sarcoidosis without CS, and 31 control subjects. Although the 6 patients with diabetic mellitus were included in the FDG-PET study of 31 patients, the average levels of plasma glucose were 98.0 ± 14.8 mg/dL in the study group and 96.6 ± 14.7 mg/dL in the control

Table 2. Clinical Background of the Patients

	sCS (n = 30)	iCS (n = 11)	P Value (sCS vs iCS)	Sarcoidosis Without CS (n = 26)
Age (y)	66.0 ± 12.9	63.5 ± 15.9	ns	64.8 ± 12.5
Sex (% male)	16.7%	63.6%	.021	23.1%
Major criteria of CS	1.8 ± 0.7	1.9 ± 0.9	ns	0.0 ± 0.2
Minor criteria of CS	1.6 ± 0.9	1.8 ± 1.0	ns	0.8 ± 0.8
Complete atrioventricular block	43.3%	36.7%	ns	0%
Limited thinning of interventricular septum	70.0%	63.6%	ns	3.9%
Left ventricular dysfunction (ejection fraction <50%)	50.0%	81.8%	ns	3.9%
Ejection fraction (%)	50.3 ± 14.5	39.8 ± 12.3	.025	67.2 ± 9.4
Gallium uptake in heart	54.5%	28.6%	ns	0%
Ventricular tachycardia	30.0%	45.5%	ns	3.8%
Focal dyskinesis	36.7%	45.5%	ns	30.8%
Diffuse hypokinesis	30.0%	45.5%	ns	3.8%
Ventricular aneurysms	13.3%	54.5%	.046	0%

CS, cardiac sarcoidosis; sCS, systemic CS; iCS, isolated CS.

Table 3. Therapeutic Background of the Patients

Prescription	sCS (n = 30)	iCS (n = 11)	*P* Value (sCS vs iCS)
Corticosteroid	76.7%	90%	ns
Initial dose of corticosteroid	22.5 ± 14.5	21.3 ± 10.4	ns
β-Blocker	43.3%	27.3%	ns
ARB	30.0%	18.2%	ns
ACE-i	20.0%	27.3%	ns
CCB	13.3%	0%	ns
Amiodarone	20.0%	63.6%	.034
Sotalol	3.3%	0%	ns
Diuretics	33.3%	63.6%	ns
Pimobendan	3.3%	18.2%	ns
Digoxin	3.3%	0%	ns
Intracardiac device	40.0%	63.6%	ns
PMI	30.0%	36.4%	ns
ICD	10.0%	63.6%	.008
CRT	0%	9.1%	ns

ARB, angiotensin II receptor antagonist; ACE-i, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; PMI, pacemaker implantation; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy.

group. Therefore, increased glucose level is not likely to have influenced the results of FDG uptake in this study. All iCS cases exhibited a focal or focal on diffuse pattern of FDG uptake. In quantitative analysis, the CVs of iCS (0.32 ± 0.09) and sCS (0.32 ± 0.13) cases were higher than those of sarcoidosis without CS cases (0.18 ± 0.06; $P = .005$ and $P = .003$, respectively) and control subjects (0.17 ± 0.06; both $P < .001$; Fig. 4, left). The associations between qualitative and quantitative data presented as the CVs of the focal pattern (0.36 ± 0.16; n = 13; $P < .001$) and the focal on diffuse pattern (0.27 ± 0.05; n = 12; $P = .001$) were higher than those of the homogeneous pattern (CV 0.19 ± 0.06). The CVs were not significantly different between the cases with the focal pattern and the focal on diffuse pattern. The CV of the homogeneous pattern was higher than that of no uptake (0.15 ± 0.06; $P = .024$; Fig. 4, right). To confirm whether sCS or iCS was present, the ROC curve of the CV demonstrated an AUC of 92.9% with a cutoff value of 0.22. At this cutoff value, the diagnostic accuracy was 92.3% for sensitivity, 80.6% for specificity, 77.4% for positive predictive value, and 93.5% for negative predictive value. In the analysis of the ratio of the highest to lowest myocardial mean SUV, the ROC curve demonstrated an AUC of 92.4% with a cutoff value of 2.1. The diagnostic accuracy was 92.3% for sensitivity, 80.6% for specificity, 77.4% for positive predictive value, and 93.5% for negative predictive value. The ROC curves were not statistically different between the 2 indices ($P = .75$; Fig. 5, left). The ratio of the highest to lowest mean SUV was strongly correlated with the CV of the mean SUV ($r = 0.96$; Fig. 5, right). The FDG-PET/CT findings of a representative iCS case are presented in Fig. 6.

Therapeutic Effect and Long-Term Survival Ratio

The ejection fraction and left ventricular diastolic dimension for sCS (n = 10) and iCS (n = 7) did not

Table 4. Characteristics of Definite or Suspected iCS

No.	Age and Sex	Group	Major Criteria of CS	Minor Criteria of CS	EMB	Systemic Reactions	Thinning Septal Wall	Focal Dyskinesis	Ventricular Aneurysm	LGE Findings/T2WI-BB		FDG-PET/CT
										Transmurality	Location	
1	72M	H	3	2	+	–	+	+ (septal)	–	NA	NA	NA
2	65F	H	2	2	+	–	+	– (diffuse)	+	Epicardium	Ventricular aneurysm	NA
3	55M	S	1	2	–	ACE, Ca	+	–	–	Midwall	Base to mid IVS	Focal on diffuse
4	66M	S	2	3	NA	–	+	– (diffuse)	–	Midepicardium	Base IVS	NA
5	71M	S	3	0	NA	ACE, Ca	+	–	–	NA	NA	Focal
6	80F	S	3	1	NA	Gallium (heart), TbT(–)	–	+ (apex)	+	NA	NA	Focal on diffuse
7	80F	S	1	2	NA	Gallium (lung), Trop	–	+ (posterior)	+	NA	NA	Focal on diffuse
8	55F	S	3	1	–	–	+	+ (septal)	+	NA	NA	Focal on diffuse
9	22M	S	2	3	–	–	+	+ (septal)	–	Midepicardium	Base to mid-IVS	NA
10	60M	S	1	3	NA	High CD4/8, TbT(–) Trop, Lyso	–	+ (posterior)	+	Midepicardium (T2WI)	Ventricular aneurysm (T2WI)	NA
11	71M	S	1	2	NA	–	–	– (diffuse)	+	NA	NA	Focal

H, histologically definite iCS; S, suspected iCS; EMB, endomyocardial biopsy; Ca, calcium; TbT, tuberculin test; Trop, troponin; CD, cluster of differentiation; Lyso, lysozyme; NA, not available; other abbreviations as in Tables 2 and 3.

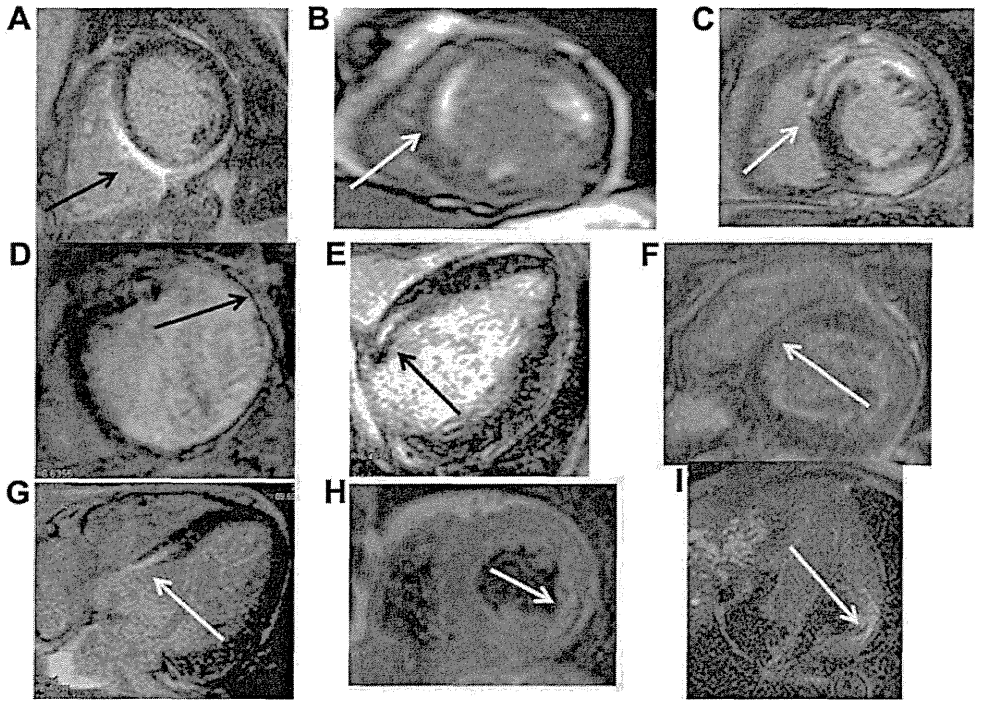

Fig. 2. Findings of late gadolinium enhancement (LGE) and T2-weighted-imaging black blood (T2WI-BB) on cardiac magnetic resonance imaging. (A) LGE in epicardial wall in short-axis view in systemic cardiac sarcoidosis (sCS) case. (B) LGE in subendocardial wall in sCS case. (C) LGE in transmural wall in sCS case. (D) Epicardial LGE pattern in the lateral aneurysmal wall in isolated cardiac sarcoidosis (iCS) case (no. 2). (E) Mid to epicardial LGE pattern in 4-chamber view in iCS case (no. 4). (F) Epicardial to midwall LGE pattern in short-axis view in iCS case (no. 9). (G) Midwall LGE pattern in iCS case (no. 3). (H) Low intensity of the epicardial posterior scar on short-axis T2WI-BB image in sCS case. (I) High intensity of myocardial edema in the posterior aneurysmal wall on 4-chamber T2WI-BB image in iCS case (no. 10).

change after prednisolone treatment (data not shown). Data on BNP level were obtained in 17 sCS cases and 7 iCS cases. The baseline BNP level was not significantly different between sCS and iCS. After prednisolone treatment, BNP level decreased significantly in both groups: sCS: 157.3 ± 130.3 pg/mL before, 108.8 ± 93.7 pg/mL

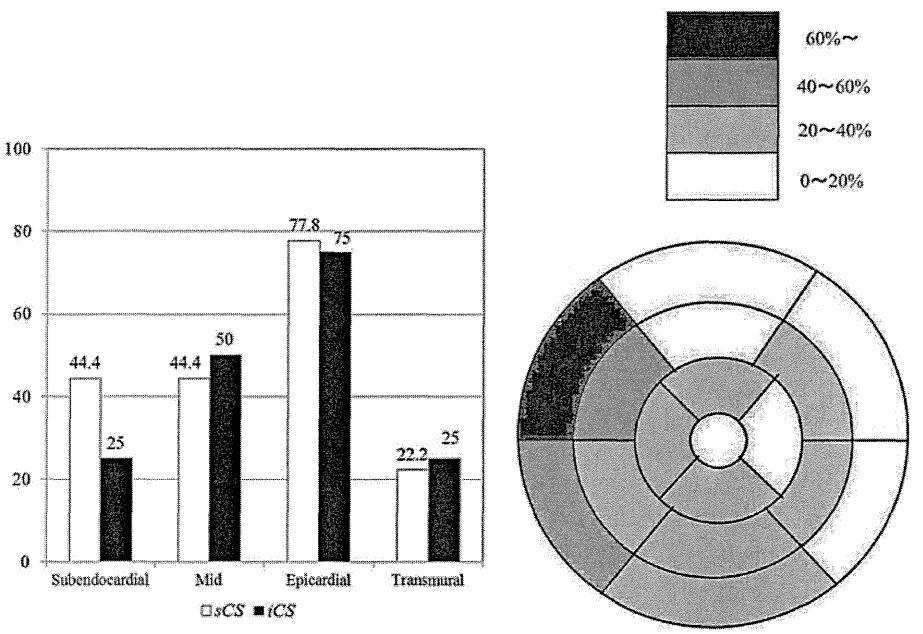

Fig. 3. The transmurality and localization of late gadolinium enhancement (LGE). Left: Transmurality of LGE was classified as subendocardial, mid, epicardial, or transmural wall. The distribution of the study cases was expressed as a percentage. Right: The rate of LGE in the 17 lesions was expressed as a percentage (black, >60%; dark gray, 40%–60%; light gray, 20%–40%; white, 0–20%).

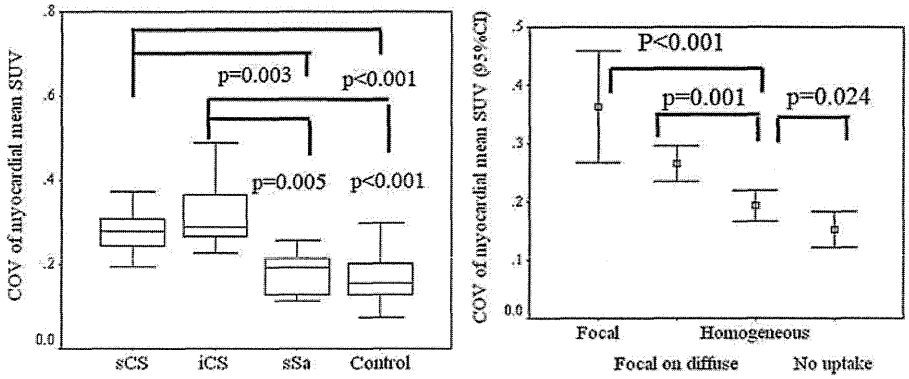

Fig. 4. Quantitative analysis with the use of coefficient of variance (CV or COV) of myocardial mean standardized uptake value (SUV) in ^{18}F-fluoro-2-deoxyglucose positron-emission tomography/computerized tomography (FDG-PET/CT). Left: Comparison of CV of mean SUV in sCS, iCS, sarcoidosis without CS (sSa), and control groups. CVs of both sCS and iCS were significantly higher than those of sSa and control groups. Right: Comparison of CV with qualitative findings of focal, focal on diffuse, homogeneous, and no-uptake patterns.

after (P = .01); iCS: 317.8 ± 331.2 pg/mL before, 138.6 ± 161.6 pg/mL after (P = .043). The mean observation time (sCS 14.3 ± 14.3 mo vs iCS 18.7 ± 11.3 mo) and mean initial prednisolone dose (sCS 27.4 ± 5.0 mg vs iCS 25.0 ± 5.0 mg) did not differ between the 2 groups. The ΔBNP of iCS was higher than that of sCS (33.3% vs 12.8%; P = .04).

The Kaplan-Meier curve indicated no difference in the long-term survival ratio between sCS and iCS. Without prednisolone treatment for CS, the prognosis was poorer (P = .0069; Fig. 7). We performed subclass analysis with and without left ventricular dysfunction and prednisolone treatment. The group with left ventricular dysfunction and without prednisolone treatment had the worst outcome among all groups (P = .0011).

Discussion

The recent report of iCS by Kandolin et al indicated that 9 (64%) of 14 patients with CS had isolated cardiac involvement without sarcoidosis of other organs.[8] However, the clinical definition of iCS and accompanying epidemiologic data have not been established. CS generally presents with a variety of myocardial and clinical symptoms of the heart. Therefore, in cases without histologic manifestation, the diagnosis and treatment of iCS are challenging, particularly when treatment with prednisolone therapy in cases of possible iCS is concerned. In the present study, we clarified the clinical characteristics of iCS cases including clinically suspected cases, investigated the therapeutic effect of prednisolone, and determined the long-term outcomes.

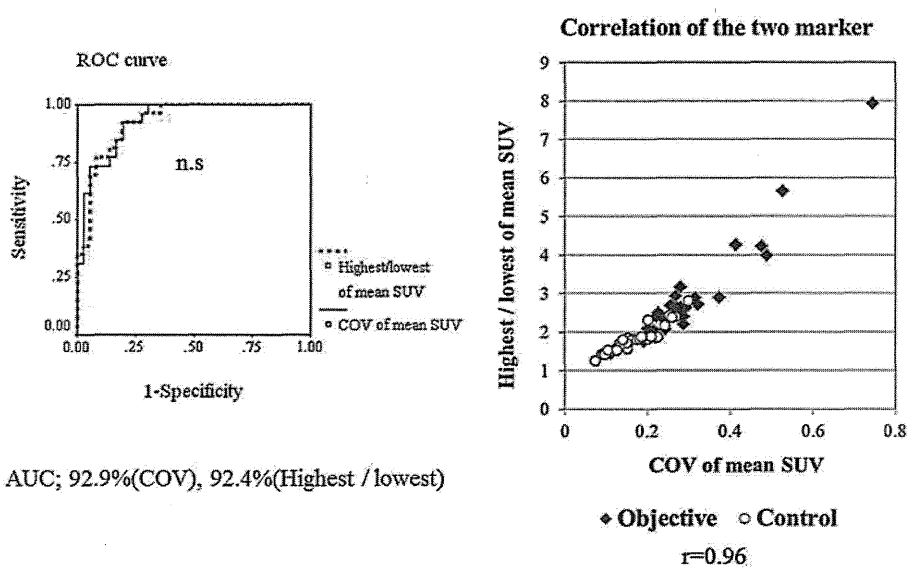

Fig. 5. Comparison of the CV and ratio of the highest to lowest mean SUV. Left: The areas under the 2 receiver operating characteristic curves were not statistically different. Right: Correlation of the CV and ratio of the highest to lowest mean SUV.

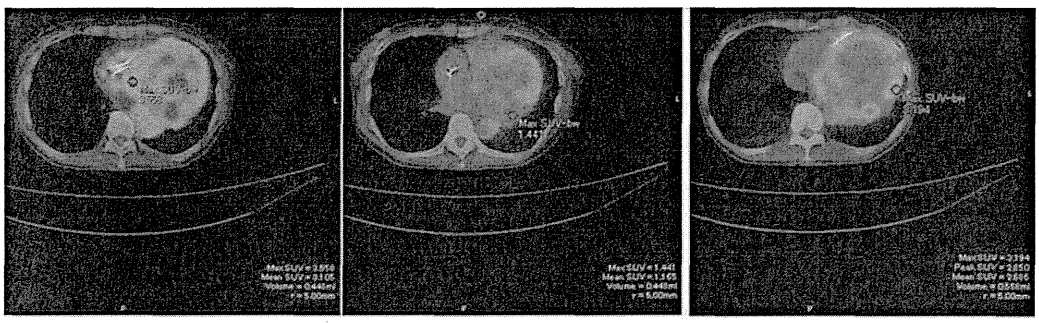

Fig. 6. FDG-PET/CT findings of a representative iCS case. A 54-year-old woman was admitted for congestive heart failure. She presented with severely low cardiac function (ejection fraction 30%) with ventricular aneurysm formation. FDG uptake demonstrated the focal on diffuse pattern. The plasma glucose level was 64 mg/dL.

However, an accurate diagnosis is critical in clinical iCS, particularly to exclude other cardiomyopathies in this series. Therefore, we focused on cardiac MRI and FDG-PET/CT, which can be used to diagnose iCS without histologic manifestations.

The myocardial tissue characteristics and LGE patterns in CS can be clearly differentiated from those of other cardiomyopathies.[17] However, LGE findings in CS cases often show polymorphic patterns with heterogeneity. In our study, LGE findings were more frequently detected in epicardial side and septal walls, and iCS was homologous to sCS regarding transmurality and localization. This specific pattern of LGE distribution should be studied further in relation to the pathologic findings.

Two iCS cases demonstrated ventricular aneurysms on cardiac MRI; 1 of these cases had LGE in the aneurysm with histologic manifestation. The other iCS case had no characteristics of the other cardiomyopathies and demonstrated myocardial edema and scar on T2WI-BB. T2WI-BB can indicate the presence of inflammation, according to a recent study.[21] Ventricular aneurysms can be caused by ischemic cardiomyopathy, hypertrophic cardiomyopathy,[22,23] and other rare conditions; however, in cases without any apparent evidence of other such causes, they can be a significant sign of CS.[24]

The assessment of myocardial FDG uptake is often a significant and controversial problem, because the physiologic conditions for glucose metabolism influence the SUV derived from FDG uptake in the myocardium.[15] Recently, fasting time of >12 hours and dietary modification (<5 g of carbohydrate restriction for the meal in the previous night) have been proposed to eliminate physiological uptake of FDG in the myocardium.[25] However, its clinical utility has not been established yet. Therefore, Japanese guidelines recommend fasting time of ≥ 12 hours for their purpose.[26] In our retrospective FDG-PET/CT study on a sufficient number of healthy control subjects, the CVs of myocardial mean SUV for the focal and focal on diffuse patterns were higher than

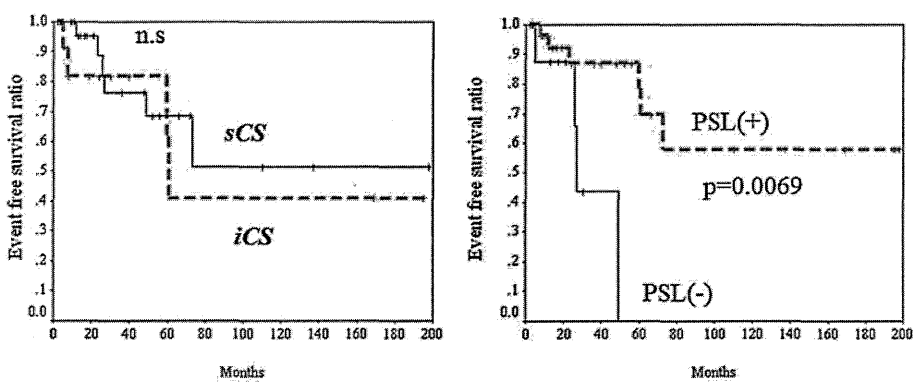

Fig. 7. Comparison of event-free curves. Left: There was no significant difference between sCS (*solid black line*) and iCS (*dashed red line*) cases. Right: The group with prednisolone treatment (*dashed red line*) had a significantly better outcome than the group without prednisolone treatment (*black line*).

those for other patterns, implying that this quantitative marker of FDG uptake was similar to the qualitative findings in the diagnosis of CS. Consequently, the CV in clinical iCS cases was equivalent to that in sCS cases.

In the analysis of the diagnostic accuracy of quantitative markers of FDG uptake, the ROC curves for CV and the ratio of the highest to lowest myocardial mean SUV demonstrated that these markers can differentiate sCS and iCS from other conditions. The utility of these 2 markers lies in the diagnosis of iCS without histologic manifestations. In particular, the measurement of the CV of myocardial SUV in 17 lesions requires time and labor; the ratio of the highest to the lowest myocardial SUV is potentially a convenient marker to assess CS quantitatively.

The incidence of iCS in CS cases was 26.8% in the present study, which is lower than that reported in an earlier study.[8] However, further research on the incidence of iCS among CS cases is required, because ethnicity-based differences in clinical manifestations have been reported.[1]

BNP level has been reported as a sensitive marker for cardiac involvement in patients with sarcoidosis.[27] In our study, BNP level decreased after prednisolone treatment in both sCS and iCS cases. However, the assessment of BNP level has limitations, because levels of the marker differ across cases and are influenced by cardioprotective drugs. We observed a significantly higher event-free survival ratio in patients who were prescribed prednisolone compared with those without prednisolone treatment, particularly in patients without left ventricular dysfunction. These results are consistent with a previous report.[6]

Thus, we attempted to determine the presence of iCS with the use of cardiac MRI and FDG-PET/CT data based on established features of CS. Our findings may be essential for establishing a technique to identify iCS without histologic manifestation.

Study Limitations

This study was a retrospective investigation performed at a single center. The number of patients was relatively low, and not all patients underwent both FDG-PET/CT and cardiac MRI during the same time period; in particular, only a few patients in the iCS group did. Endomyocardial biopsy was performed in only a portion of iCS cases. The enrollment of a greater number of iCS cases based on histologic diagnosis is necessary to assess the utility of cardiac MRI and FDG-PET in the determination of iCS. Otherwise, as previously stated, the sensitivity of endomyocardial biopsy can be reduced by sampling errors. In our study, the sensitivity of the biopsy was 22.2%. This rate is consistent with a past report[11] and supports the suggestion that CS diagnosis should not depend exclusively on histologic findings.

The recruitment of iCS cases may have led to some bias because we assessed iCS cases by means of conventional guidelines. Moreover, the iCS cases included in the present study may be more severe in terms of cardiac function compared with iCS cases overall; because we included only symptomatic patients in the present study, none of the patients had an early phase of the condition. The disease activity of CS is difficult to assess because of the low grade of chronic inflammation, even though it can influence the sensitivity of imaging data. FDG-PET may be useful in the detection of inflammation in CS cases. The criteria for disease activity in CS are not yet known, and this issue will be a significant target of further research. The effect of corticosteroids on long-term prognosis could not be confirmed from the present data because their were only 11 definite or suspected iCS patients.

Conclusion

In the present study, we noted that the findings of definite or suspected iCS cases were similar to those of sCS cases. From these data, we propose the use of these noninvasive imaging modalities for diagnosing iCS without histologic manifestation to avoid the underdiagnosis of treatable cases. Further evaluation for the clinical definition of iCS is mandatory.

Disclosures

None.

Acknowledgments

The authors thank Go Haraguchi, MD, PhD, Takeshi Sasaki, MD, PhD, Mihoko Kawabata, MD, PhD, and Tetsuo Sasano, MD, PhD, at the Department of Cardiovascular Medicine of Tokyo Medical and Dental University, Setsu Gomi, Takahiro Hamanaka, Kota Nakae, Makiko Hayashi, Yuuji Kojima, Mia Takahashi, Takashi Sugaya, Shin-ichi Ohtani, and Yasushi An-naka (radiologic technologists, Tokyo Medical and Dental University); Nozomu Koyama and Tadashi Kishida (radiologic technologists, Cardiovascular Imaging Clinic); Rumiko Torigoe, Seiko Shimizu, and Sachiko Isono (technical advisers, Toshiba Medical Systems); and Chris Maschio.

References

1. Lannuzzi MC, Rybicki BA, Teirstein AS. Medical progress: sarcoidosis. N Engl J Med 2007;357:2153–65.
2. Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. Am J Med 1977;63:86–108.
3. Sekiguchi M, Numao Y, Imai M, Furuie T, Mikami R. Clinical and histologic profile of sarcoidosis of the heart and acute idiopathic myocarditis. Jpn Circ J 1980;44:249–63.
4. Diagnostic standard and guidelines for sarcoidosis. Jpn J Sarcoidosis *Granulomat*ous Disord 2007;27:89–102.
5. Silverman KJ, Hutchins GM, Buckley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 1978;58:1204–11.
6. Yazaki Y, Isobe M, Hiroe M, Morimoto M, Hiramatsu S, Nakano T, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisolone. Am J Cardiol 2001;88:1006–10.

7. Kosuge H, Noda M, Kakuta T, Kishi Y, Isobe M, Numano F. Left ventricular apical aneurysm in cardiac sarcoidosis. Jpn Heart J 2001;42:265–9.
8. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arryhythm Electrophysiol 2011;4:303–9.
9. Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivisto SM, et al. Diagnosing isolated cardiac sarcoidosis. J Intern Med 2011;270:461–8.
10. Isobe M, Tezuka D. Isolated cardiac sarcoidosis: Clinical characteristics, diagnosis and treatment. Int J Cardiol 2015;182:132–40.
11. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: Evaluation of endomyocardial biopsies. Am Heart J 1999;138:299–302.
12. Sekiguchi M, Yazaki Y, Isobe M, Hiroe M. Cardiac sarcoidosis: diagnostic, prognostic, and therapeutic consideration. Cardiovasc Drugs Ther 1996;10:495–510.
13. Baba Y, Kubo T, Kitaoka H, Okawa M, Yamanaka S, Kawada Y, et al. Usefulness of high-sensitive cardiac troponin T for evaluating the activity of cardiac sarcoidosis. Int Heart J 2012;53:287–92.
14. Smedema JP, Snoep G, Kroonenburgh MPG, Geuns RJ, Dassen WRM, Gorgels APM, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 2005;45:1683–90.
15. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M, et al. Focal uptake on ^{18}F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005;26:1538–43.
16. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischemic cardiomyopathies. Eur Heart J 2005;26:1461–74.
17. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation 2009;120:1969–77.
18. Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, et al. Role of FDG PET-CT in Takayasu Arteritis. Sensitive Detection of Recurrences. J Am Coll Cardiol Img 2012;5:422–9.
19. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.
20. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H, et al. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. JACC Cardiovasc Imaging 2010;3:1219–28.
21. Yang Y, Safka K, Graham JJ, Roifman I, Zia MI, Wright GA, et al. Correlation of late gadolinium enhancement MRI and quantitative T2 measurement in cardiac sarcoidosis. J Magn Reson Imaging 2014;39:609–16.
22. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, et al. Prevalence, clinical significance, and natural history of left ventricular apical aneurysm in hypertrophic cardiomyopathy. Circulation 2008:118:1541–9.
23. Matsubara K, Nakamura T, Kuribayashi T, Azuma A, Nakagawa M. Sustained cavity obliteration and apical aneurysm formation in apical hypertrophic cardiomyopathy. J Am Coll Cardiol 2003;42:288–95.
24. Haraki T, Ueda K, Shintani H, Hayashi T, Taki J, Mabuchi H. Spontaneous development of left ventricular aneurysm in a patient with untreated cardiac sarcoidosis. Circ J 2002;66:519–21.
25. Ohira H, Tsujino I, Yoshinaga K. ^{18}F-Fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. Eur J Nucl Med Mol Imaging 2011;38:1773–83.
26. Ishida Y, Yoshinaga K, Miyagawa M, Moroi M, Kondoh C, Kiso K, et al. Recommendations for ^{18}F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. Ann Nucl Med 2014;28:393–403.
27. Yasutake H, Seino Y, Kashiwagi M, Honma H, Matsuzaki T, Takano T. Detection of cardiac sarcoidosis using cardiac markers and myocardial integrated backscatter. Int J Cardiol 2005;102:259–68.

ORIGINAL ARTICLE

Cardiopulmonary Exercise Testing as a Tool for Diagnosing Pulmonary Hypertension in Patients with Dilated Cardiomyopathy

Akihiro Hirashiki, M.D., Ph.D.,* Takahisa Kondo, M.D., Ph.D.,* Takahiro Okumura, M.D., Ph.D.,† Yoshihiro Kamimura, M.D.,† Yoshihisa Nakano, M.D.,† Kenji Fukaya, M.D.,† Akinori Sawamura, M.D.,† Ryota Morimoto, M.D.,† Shiro Adachi, M.D.,† Kyosuke Takeshita, M.D., Ph.D.,† and Toyoaki Murohara, M.D., Ph.D.†

*From the *Department of Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, Nagoya, Japan and †Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Background: Recently, it has become increasingly recognized that pulmonary hypertension (PH) is a particularly threatening result of left-sided heart disease. However, there have been few investigations of the impact of cardiopulmonary exercise testing (CPX) variables on PH in dilated cardiomyopathy (DCM). We evaluated the usefulness of crucial CPX variables for detecting elevated pulmonary arterial pressure (PAP) in patients with DCM.

Methods: Ninety subjects with DCM underwent cardiac catheterization and CPX at our hospital. Receiver operator characteristic (ROC) analysis was performed to assess the ability of CPX variables to distinguish between the presence and absence of PH.

Results: Overall mean values were: mean PAP (mPAP), 18.0 ± 9.6 mmHg; plasma brain natriuretic peptide, 233 ± 295 pg/mL; and left ventricular ejection fraction, 30.2 ± 11.0%. Patients were allocated to one of two groups on the basis of mean PAP, namely DCM without PH [mean PAP (mPAP) <25 mmHg; $n = 75$] and DCM with PH (mPAP ≥25 mmHg; $n = 15$). A cutoff achieved percentage of predicted peak VO_2 (%PPeak VO_2) of 52.5% was the best predictor of an mPAP ≥25 mmHg in the ROC analysis (area under curve: 0.911). In the multivariate analysis, %PPeak VO_2 was the only significant independent predictor of PH (Wald 6.52, odds ratio 0.892, 95% CI 0.818–0.974; P = 0.011).

Conclusions: %PPeak VO_2 was strongly associated with the presence of PH in patients with DCM. Taken together, these findings indicate that CPX variables could be important for diagnosing PH in patients with DCM.

Ann Noninvasive Electrocardiol 2016;00(0):1–9

cardiopulmonary exercise testing; dilated cardiomyopathy; peak VO_2; pulmonary hypertension

Pulmonary hypertension (PH) occurs commonly in patients with left heart disease and is associated with increased morbidity and mortality.[1,2] PH associated with left heart disease is classified in group 2 of the Nice 2013 classification.[2] and is believed to be the most common form of PH,[3] with both passive and active components.[1,4] In patients with ischemic or nonischemic dilated cardiomyopathy

Address for correspondence: Takahisa Kondo, Department of Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466–8550, Japan. Tel/Fax: +81-52-744-0388; E-mail: takahisa@med.nagoya-u.ac.jp

DOI:10.1111/anec.12308

(DCM), the presence of PH is also a predictor of morbidity or mortality.[5] We previously reported that the presence of PH provides valuable prognostic information in ambulatory patients with DCM.[6]

Cardiopulmonary exercise testing (CPX) is an established assessment tool in heart failure (HF) populations.[7] Most often, CPX is used to assess prognosis in HF patients being considered for heart transplantation.[8] and to provide an additional evaluation of disease severity.[7] Given the emerging importance of detecting PH in HF patients and the already established role of CPX in this patient population, examining the ability of this exertional assessment to unmask elevated pulmonary arterial pressure (PAP) is an important research endeavor. CPX has already been proved useful for diagnosing secondary PH in other patients, such as those with hypertrophic cardiomyopathy.[9] or HF.[10,11] However, to our knowledge, there have been no investigations of the impact of CPX variables on PH in DCM. Here, we therefore aimed to evaluate the usefulness of crucial CPX variables for detecting elevated PAP in patients with DCM.

METHODS

Study Population

A total of 90 consecutive ambulatory patients with DCM (62 men (69%); mean age ± SD, 52 ± 13 years) were enrolled retrospectively in the study at Nagoya University Hospital, Japan. All patients were on optimal pharmacological therapy according to current guidelines for the treatment of HF.[12] Individuals who had suffered an episode of acute HF within the previous month, who had renal dysfunction [estimated glomerular filtration rate (eGFR) <30 mL min^{-1} 1.73 m^{-2}], or who had received an implanted cardiac resynchronization therapy device or an implantable cardioverter defibrillator before cardiac catheterization were excluded from the study. Echocardiographic findings as a screening tool were left ventricular (LV) dilatation and systolic dysfunction, as defined by depressed LV ejection fraction. DCM was defined by the presence of both an LV ejection fraction of <50% (as revealed by contrast left ventriculography) and dilation of the LV cavity in the absence of coronary artery stenosis of >50% (as determined by coronary angiography), valvular heart disease, arterial hypertension, and secondary cardiac muscle disease attributable to any known systemic condition.[13] No patients had histories of acute viral myocarditis or familial DCM, or evidence of immune triggers. The study protocol complied with the Declaration of Helsinki, and written informed consent was obtained from each study patient. The study protocol was approved by the Ethics Review Board of Nagoya University School of Medicine (approval no. 359).

Study Protocol

Physical examination, laboratory measurements, CPX, and biventricular catheterization were performed within 3 days of study enrollment. All patients were in a stable condition at the time of testing.

Cardiac Catheterization

All patients initially underwent diagnostic right and left heart catheterization. Patients were in a stable condition at the time of catheterization. For hemodynamic assessment, a 6F Swan-Ganz catheter (Goodman Biosensors, Tokyo, Japan) was inserted by using a jugular approach. Coronary angiography and left ventriculography via the right radial artery were also performed. A 6F fluid-filled pigtail catheter with a high-fidelity micromanometer (CA-61000-PLB Pressure-tip Catheter; CD Leycom, Zoetermeer, The Netherlands) was positioned in the left ventricle to measure LV pressure. Endomyocardial biopsy was performed in all patients to exclude myocarditis and specific heart muscle disease. Biopsy specimens were obtained from the septal wall of the right ventricle with a 6F bioptome.

Diagnosis of PH

PH was defined hemodynamically as a mean PAP (mPAP) of ≥25 mmHg at rest, as assessed by right heart catheterization without inhalation of nitric oxide and supplemental oxygen. Mean PAP, mean right atrial pressure, mean pulmonary artery wedge pressure, and the respective oxygen saturations, along with those in the main pulmonary artery, were measured. Cardiac output was assessed by thermodilution and was expressed in liters per minute.

CPX Procedure

Each patient underwent CPX at a progressively increasing work rate to maximal tolerance on a cycle ergometer. The test protocol was in accordance with the recommendations of the American Thoracic Society and American College of Chest Physicians.[14] The oxygen and carbon dioxide sensors were calibrated before each test by using gases with known oxygen, nitrogen, and carbon dioxide concentrations. The flow sensor was also calibrated before each test by using a 3-L syringe. All patients started at 10 W for a 3-min warm-up, followed by a 10-W/min ramp increment protocol up to the termination criteria. Test termination criteria consisted of patient request, volitional fatigue, ventricular tachycardia, ≥2 mm horizontal or downsloping ST-segment depression, or a drop in systolic blood pressure (BP) of ≥20 mmHg during exercise. A qualified exercise physiologist conducted each test, with physician supervision. A 12-lead electrocardiogram was monitored continuously, and BP was measured every minute during exercise and throughout the recovery period. Respiratory gas exchange variables, including VO_2, VCO_2, and minute ventilation (VE), were acquired continuously throughout the exercise testing by using an Oxycon Pro ergospirometer (Care Fusion; San Diego, CA, USA); gas-exchange data were obtained breath-by-breath. Peak VO_2 was expressed as the highest 30-s average value obtained during the last stage of the exercise test, and the peak respiratory exchange ratio was the highest 30-s average value during the last stage of the test. The VE/VCO_2 slope was determined by using linear regression analysis of the VE and VCO_2 obtained during exercise.[15] Exercise oscillatory ventilation (EOV) was assessed by using the criteria previously reported by Leite et al.[16] The achieved percentage of predicted peak VO_2 (%PPeak VO_2) was calculated as [obtained peak VO_2 / age-, gender-, and weight-adjusted predicted peak VO_2 in mL min^{-1} kg^{-1}] × 100.[17,18] The ratio of the increase in VO_2 to the increase in work rate (WR) [$\Delta O_2/\Delta WR$] was calculated by least-squares linear regression from the data recorded between 30 s after the start of incremental exercise and 30 s before the end of exercise.

Statistical Analysis

Data are presented as means ± SD. Variables were compared between the DCM with PH and DCM without PH groups by using Student's *t*-test for unpaired data. The chi-square test was used to assess the significance of differences between dichotomous variables. The impact of mPAP on outcome was analyzed by using the presence or absence of PH as a categorical determinant of adverse events. Other baseline predictors of events were determined by performing univariate Cox proportional hazard regression analysis with age, gender, creatinine, plasma brain natriuretic peptide (BNP), heart rate, cardiac index, systolic BP, LV end-diastolic pressure, pulmonary arterial wedge pressure, pulmonary vascular resistance, peak VO_2, and VE/VCO_2 slope as potential determinants. The hazard ratio and 95% confidence interval were defined. Receiver-operator characteristic (ROC) curve analysis was used to assess the ability of CPX variables to identify subjects with an mPAP ≥25 mmHg. Binary logistic regression assessed the univariate and multivariate (with $P < 0.1$) ability of CPX variables to identify subjects with mPAP ≥25 mmHg. All analyses were performed with the SPSS 17.0 software package (SPSS, Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The mean age was 52 years, and 69% of subjects were male. At the time of cardiac catheterization, beta blockers were used by 87% of all patients, angiotensin-converting-enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs) by 86%, diuretics by 69%, and spironolactone by 46%. The mean (25th, 75th percentile) plasma BNP level was 233 (55, 306) pg/mL, and the mean LV ejection fraction was 30.2 ± 11.0%.

Clinical characteristics and important hemodynamic parameters of all patients are shown in Table 1. Subjects were allocated to one of two groups on the basis of the absence (DCM without PH group, $n = 75$) or presence (DCM with PH group, $n = 15$) of PH. PH was present in 17% of patients with DCM, and the median (25th, 75th percentile) mPAP for all DCM patients was 17.9 (11.8, 20.0) mmHg. DCM patients with PH were significantly younger than those without PH. Diuretics, beta-blockers, and spironolactone were used significantly more frequently in DCM with PH than in DCM without PH, but there

Table 1. Patient Characteristics

	DCM without PH (n = 75)	DCM with PH (n = 15)	P
Age (years)	54 ± 13	45 ± 14	0.038
Male (n, %)	53 (71)	9 (60)	0.459
BMI (kg/m^2)	23.5 ± 4.2	21.6 ± 4.1	0.133
NYHA	1.57 ± 0.76	2.50 ± 1.23	0.131
Medication			
Diuretics (n, %)	47 (63)	15 (100)	<0.001
ACE-I/ARBs (n, %)	63 (84)	14 (93)	0.753
β-Blockers (n, %)	63 (84)	15 (100)	<0.001
Digitalis (n, %)	9 (12)	9 (17)	0.710
Statins (n, %)	9 (12)	1 (7)	0.669
Amiodarone (n, %)	7 (9)	5 (33)	0.271
Spironolactone (n, %)	29 (39)	12 (80)	0.002
Laboratory			
BNP (pg/mL)	175 (37–274)	550 (178–840)	0.013
eGFR (mL/min/1.73 m^2)	72 ± 26	74 ± 15	0.707
Hb (mg/dL)	14.0 ± 1.6	14.0 ± 2.3	0.962
T. Chol (mg/dL)	194 ± 34	175 ± 46	0.152
TG (mg/dL)	156 (77–177)	111 (68–152)	0.046
HbA1c (%)	5.74 ± 1.15	5.63 ± 0.80	0.648
Cardiac catheterization			
PAWP (mmHg)	10.0 ± 4.6	25.3 ± 6.9	<0.001
Systolic PAP (mmHg)	24.2 ± 6.8	49.0 ± 15.4	<0.001
Diastolic PAP (mmHg)	9.5 ± 4.0	28.8 ± 10.0	<0.001
Mean PAP (mmHg)	14.4 ± 4.3	35.5 ± 9.6	<0.001
PVR (Wood units)	0.96 ± 0.92	3.25 ± 2.64	0.005
RAP (mmHg)	5.0 ± 3.1	7.7 ± 2.6	0.018
SvO_2 (%)	71.8 ± 5.8	61.8 ± 7.3	0.024
TPG (mmHg)	4.4 ± 4.0	10.3 ± 5.7	0.002
DPG (mmHg)	−0.5 ± -0.6	3.5 ± 3.2	<0.001
Heart rate (bpm)	76.5 ± 13.1	85.0 ± 23.9	0.303
Cardiac output (L/min)	4.73 ± 1.20	3.75 ± 1.46	0.025
Cardiac index (L/min/m^2)	2.75 ± 0.59	2.27 ± 0.69	0.022
Systolic BP (mmHg)	122 ± 19	104 ± 30	0.051
Diastolic BP (mmHg)	74 ± 12	70 ± 14	0.287
LVEDP (mmHg)	14.4 ± 7.1	25.1 ± 8.8	0.001
LVEDVI (ml/m^2)	129.5 ± 41.3	183.7 ± 65.4	0.004
LVESVI (ml/m^2)	90.6 ± 37.8	150.1 ± 59.2	0.004
LVEF (%)	32.0 ± 10.1	22.7 ± 10.4	0.001

Data are presented as mean values ± SD and medians [interquartile range or n (%)].
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; DCM = dilated cardiomyopathy; DPG = diastolic pulmonary vascular gradient; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; LVEDP = LV end-diastolic pressure; LVEDVI = LV end-diastolic volume index; LVESVI = LV end-systolic volume index; LVEF = LV ejection fraction; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation; T. Chol = total cholesterol; TG = triglyceride; TPG = transpulmonary pressure gradient.

were no differences between the 2 groups in the use of ACE-Is or ARBs at the time of cardiac catheterization. Although plasma BNP levels were significantly higher in DCM with PH, eGFR, and serum hemoglobin levels did not differ between the two groups. On cardiac catheterization, the systolic, diastolic, and mean PAP, as well as the pulmonary vascular resistance and right arterial pressure, were significantly higher in DCM with PH than in DCM without PH, whereas the cardiac index and mixed venous oxygen saturation were significantly lower in the former group. LV end-diastolic pressure, LV end-diastolic volume index, and LV end-systolic volume index were significantly higher, and LV ejection fraction was significantly lower, in DCM with PH.

Table 2. Hemodynamic Parameters in Cardiopulmonary Exercise Testing

	DCM without PH (n = 75)	DCM with PH (n = 15)	P
Exercise duration (min)	7.5 ± 2.5	7.1 ± 3.9	0.671
Peak VO_2 (ml/kg/min)	19.2 ± 4.8	11.3 ± 3.6	<0.001
%PPeak VO_2 (%)	72.0 ± 21.8	40.6 ± 12.8	<0.001
VE/VCO_2 slope	29.2 ± 7.4	38.6 ± 9.7	0.002
Peak VO_2/HR ratio	10.1 ± 4.6	6.9 ± 3.4	0.005
$\Delta VO_2/\Delta WR$	9.7 ± 3.8	5.5 ± 3.1	<0.001
Resting HR (bpm)	85 ± 19	88 ± 17	0.60
Peak HR (bpm)	133 ± 29	117 ± 21	0.019
Resting systolic BP (mmHg)	121 ± 22	111 ± 30	0.212
Peak systolic BP (mmHg)	161 ± 36	131 ± 45	0.026
Resting $P_{ET}CO_2$ (mmHg)	33.3 ± 6.4	30.4 ± 3.7	0.112
EOV	23 (31%)	7 (47%)	0.231
Peak RER	1.09 ± 0.08	1.07 ± 0.11	0.332

BP = blood pressure; HR = heart rate; EOV = exercise oscillatory ventilation; %PPeak VO_2 = achieved percentage of predicted peak VO_2; $P_{ET}CO_2$ = end-tidal carbon dioxide tension; RER = respiratory exchange ratio; $\Delta VO_2/\Delta WR$ = ratio of change in VO_2 to change in work rate.

The CPX variables are shown in Table 2. Although exercise duration did not differ between the two groups, peak VO_2, %PPeak VO_2, peak VO_2/HR ratio, and $\Delta VO_2/\Delta WR$ were significantly lower in DCM with PH than in DCM without PH. VE/VCO_2 slope was significantly higher in DCM with PH than in DCM without PH. Although resting HR and resting systolic BP did not differ significantly between the two groups, peak HR and peak systolic BP were significantly lower in DCM with PH than in DCM without PH.

CPX Variables for Detecting PH

We performed an ROC curve analysis of the ability of peak VO_2, %PPeak VO_2, VE/VCO_2 slope, and $\Delta VO_2/\Delta WR$ to detect mPAP ≥25 mmHg (Fig. 1). All four diagnostic models were significant for detecting mPAP ≥25 mmHg. A %PPeak VO_2 cutoff value of 52.5% was the best predictor of mPAP ≥25 mmHg in the ROC analysis (area under the curve [AUC: 0.911]; 95% confidence interval [CI]: 0.846 to 0.977, P < 0.001). The sensitivity and specificity of using %PPeakVO_2 to detect PH were 82.8% and 85.7%, respectively. The sensitivity and specificity with a peak VO_2 cutoff value of 13.55 mL kg^{-1} min^{-1} were 90.6% and 71.4%, respectively (AUC: 0.904; 95% CI: 0.832 to 0.976, P < 0.001). A VE/VCO_2 slope cutoff value of 31.01 had significant diagnostic value (AUC: 0.801; 95% CI: 0.681 to 0.920, P < 0.001), and a $\Delta VO_2/\Delta WR$ cutoff value of 7.79 also had significant diagnostic value (AUC: 0.841; 95% CI: 0.714 to 0.968, P < 0.001) for detecting PH.

We used binary logistic regression to assess the independent and combined abilities of CPX variables for detecting PH (Table 3). In the univariate analysis, peak VO_2, %PPeak VO_2, peak VO_2/HR ratio, VE/VCO_2 slope, $\Delta VO_2/\Delta WR$, peak systolic BP, and rest $P_{ET}CO_2$ were significant predictors of PH. In the multivariate analysis, %PPeak VO_2 was the only significant independent predictor of PH (Wald 6.52, odds ratio 0.892, 95% CI 0.818 to 0.974; P = 0.011).

DISCUSSION

Here, we reported for the first time that reduced %PPeak VO_2 was strongly associated with the presence of PH in patients with DCM. Other CPX variables, including peak VO_2, VE/VCO_2 slope, and $\Delta VO_2/\Delta WR$, were also useful for detecting the presence of PH. Taken together, these results indicate that CPX variables could be important for diagnosing PH in patients with DCM.

Usefulness of Exercise Capacity for Detecting PH in DCM

Four CPX variables, namely peak VO_2, %PPeak VO_2, $\Delta VO_2/\Delta WR$, and VE/VCO_2 slope (see Fig. 1), were especially strong predictors of PH. Peak VO_2 and %PPeakVO_2 were superior to the other two as diagnostic markers of increased mPAP. In addition, %PPeak VO_2 was the only significant independent

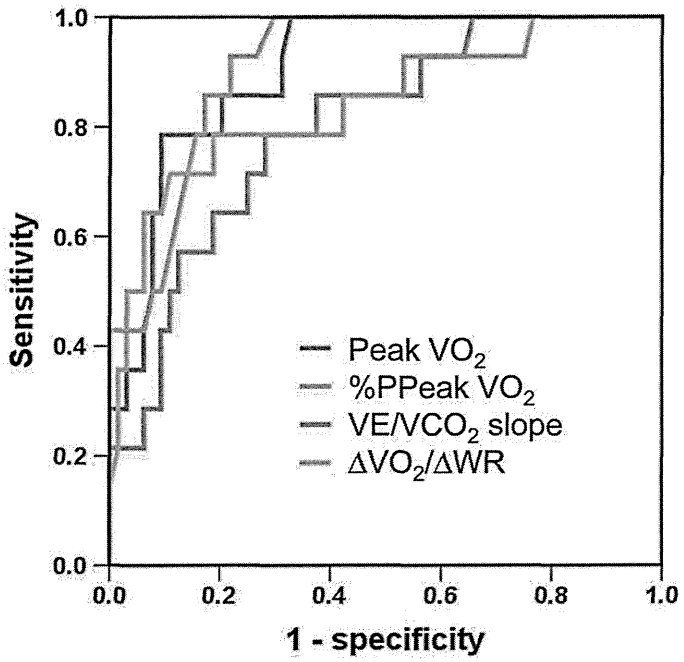

Figure 1. Receiver operating characteristic (ROC) curves showing the ability of cardiopulmonary exercise testing variables to detect pulmonary hypertension (PH). ROC curves of the abilities of peak VO_2, %PPeak VO_2, VE/VCO_2 slope, and $\Delta VO_2/\Delta WR$ to detect PH (i.e., mPAP ≥25 mmHg). AUC = area under the curve; CI = confidence interval; %PPeak VO_2 = achieved percentage of predicted peak VO_2; WR = work rate.

Table 3. Binary Logistic Analysis for the Detection of Pulmonary Hypertension

	Univariate				Multivariate			
Analysis	**Wald**	**OR**	**95%CI**	**P**	**Wald**	**OR**	**95%CI**	**P**
Peak VO_2 (mL/kg/min)	15.1	0.672	0.550–0.821	<0.001				
%PPeak VO_2 (%)	14.0	0.902	0.854 –0.952	<0.001	6.52	0.892	0.818–0.974	0.011
Peak VO_2/HR ratio	7.13	0.744	0.600 –0.924	0.008				
VE/VCO_2 slope	11.6	1.136	1.056 –1.222	0.001				
$\Delta VO_2/\Delta WR$	13.9	0.609	0.470 –0.790	<0.001				
Peak HR (bpm)	3.81	0.979	0.959 –1.000	0.051				
Peak systolic BP (mmHg)	6.62	0.976	0.958 –0.994	0.010				
EOV	0.52	1.023	0.726 –1.370	0.528				
Rest $P_{ET}CO_2$ (mmHg)	6.99	0.862	0.772 –0.962	0.008				
Peak W (watts)	0.47	0.993	0.974 –1.013	0.490				

CI = confidence interval; OR = odds ratio. Other abbreviations as in Tables 1 and 2.

predictor of PH by the multivariate logistic analysis (see Table 3).

Peak VO_2 has traditionally been considered a "gold standard" for selecting candidates for cardiac transplantation.[8] In contrast, %PPeakVO_2 is age-, gender-, and weight-adjusted and is based on directly measured peak VO_2 during CPX. Furthermore, %PPeak VO_2 provides important information that can be used for risk stratification of patients with HF.[19] %PPeak VO_2 and peak VO_2 had similar abilities to detect PH by ROC analysis, but %PPeak VO_2 was the only significant independent predictor of PH by the multivariate logistic analysis in our patients.

DCM patients range in age and tend to be younger than other HF patients; this was certainly the case in our DCM patients. The combination of reduced LV ejection fraction and relatively young age at onset suggests that DCM occurrence is at least partly influenced by genetic factors,[20]

although our study did not include genetic profiling to support this hypothesis. These patients are at risk of developing severe, refractory HF. From this perspective, %PPeak VO_2 might be a more useful predictor of PH than other CPX variables, including peak VO_2 in DCM because it is adjusted for age.

In patients with HF, the ventilatory parameters in CPX can reflect reactive PH.[11] VE/VCO_2 slope or EOV is important for diagnosing PH in hypertrophic cardiomyopathy,[9] and HF, including with normal ejection fraction,[10] or ischemia.[11] We considered that the main reason for the difference between these studies.[10,11] and our study was different study populations. In addition, the mechanisms behind the occurrence of a steep VE/VCO_2 slope and the presence of EOV are multifactorial. Abnormalities of ventilatory reflex control and pulmonary hemodynamics, as well as the presence of a low cardiac index, during exercise are all possible causes.[16,21,22] In our study, VE/VCO_2 slope (see Fig. 1), but not EOV (AUC: 0.625; 95% CI: 0.427 to 0.823, P = 0.211), was a significant parameter for detecting PH in the ROC analysis. Similarly, VE/VCO_2 slope, but not EOV, was a significant predictor of PH in the univariate analysis (see Table 3). EOV was assessed by using the criteria previously reported by Leite et al.[16] Defining EOV can be complex and difficult during exercise; further investigations are needed to determine whether it can be used to detect PH in DCM.

Parameters obtained during submaximal exercise have an advantage over peak VO_2 in that they can be obtained without maximum effort. In addition, measurement of peak VO_2 depends on the subject's motivation and is easily influenced by the bias of the investigator. $\Delta VO_2/\Delta WR$ and VE/VCO_2 slope are characterized by the time course of change in respiratory gas variables, reflecting the ability of cardiopulmonary function to adapt to increasing work rate. $\Delta VO_2/\Delta WR$ and VE/VCO_2 slope may therefore, in some regards, be useful in addition to peak VO_2 for assessing PH.

Clinical Implications

Exercise tolerance reflects a number of important prognostic factors, including cardiac function, oxygen-carrying capacity, and autonomic nervous system balance.[23-25] CPX is a diagnostic tool used to detect serial changes in exercise capacity. It is of particular benefit for assessing peak VO_2 and VE/VCO_2 slope in patients with chronic HF, because these parameters function as predictors of overall mortality or determinants of risk stratification in such individuals.[26-30]

The recognition of PH due to left heart disease has created the need for diagnostic tests to determine when a patient's PAP is elevated. CPX variables have already been evaluated by echocardiography to detect systolic PAP ≥40 mmHg in an HF population.[10] Determination of systolic PAP echocardiographically by using the sum of the peak RV-RA (right ventricular - right atrial) pressure gradient and the RA pressure has been established as reliable,[31] but additional studies have questioned the accuracy of this relationship, particularly at higher pulmonary artery pressures.[32,33] In patients with very severe tricuspid regurgitation, the Doppler envelope may be truncated because of the early equalization of RV and RA pressures, and using a simplified Bernoulli equation may underestimate the RV-RA gradient.[34]

Here, we examined resting hemodynamic variables, gold standard method, by cardiac catheterization. The use of CPX to diagnose secondary PH has already been demonstrated.[9,35] However, to our knowledge, this is the first study to have investigated the ability of crucial CPX variables to detect elevated PAP.

Currently, there is no specific therapy for PH due to left heart disease. All of our study patients who had DCM with PH used various combinations of diuretics and beta blockers. In addition, 80% of them were using spironolactone at the time of cardiac catheterization; we therefore considered that these patients were optimally medicated. Using CPX to detect PH may lead to early therapeutic interventions for DCM.

Study Limitations

This was a retrospective study in a single center and with a relatively small sample size. Moreover, hemodynamic diagnosis by challenge tests such as exercise and acute pulmonary vasoreactivity testing was not performed. Finally, the use of single time point measurements did not allow us to assess the time-dependence of PAP in the Cox regression analysis and may have led us to underestimate the prognostic significance of PH.

CONCLUSIONS

%PPeak VO_2 was strongly associated with the presence of PH in patients with DCM. Peak VO_2,

VE/VCO_2 slope, and $\Delta VO_2/\Delta WR$ were also useful for detecting the presence of PH. Taken together, these findings indicate that CPX variables could be important for diagnosing PH in patients with DCM.

Acknowledgments: *This work was supported in part by grants-in-aid from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan.*

Disclosures

Takahisa Kondo and Akihiro Hirashiki are affiliated with a university department that receives funding from Actelion Pharmaceuticals Japan.

REFERENCES

1. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975–990.
2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34–41.
3. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43–54.
4. Fang JC, DeMarco T, Givertz MM, et al. World Health Organization Pulmonary Hypertension group 2: Pulmonary hypertension due to left heart disease in the adult—a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2012;31:913–933.
5. Abramson SV, Burke JF, Kelly JJ, et al. Pulmonary hypertension predicts mortality and morbidity in patients with dilated cardiomyopathy. Ann Intern Med 1992;116: 888–895.
6. Hirashiki A, Kondo T, Adachi S, et al. Prognostic value of pulmonary hypertension in ambulatory patients with non-ischemic dilated cardiomyopathy. Circ J 2014;78: 1245–1253.
7. Balady GJ, Arena R, Sietsema K, et al. Clinician's Guide to cardiopulmonary exercise testing in adults: A scientific statement from the American Heart Association. Circulation 2010;122:191–225.
8. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778–786.
9. Arena R, Owens DS, Arevalo J, et al. Ventilatory efficiency and resting hemodynamics in hypertrophic cardiomyopathy. Med Sci Sports Exerc 2008;40:799–805.
10. Guazzi M, Cahalin LP, Arena R. Cardiopulmonary exercise testing as a diagnostic tool for the detection of left-sided pulmonary hypertension in heart failure. J Card Fail 2013;19:461–467.
11. Lim HS, Theodosiou M. Exercise ventilatory parameters for the diagnosis of reactive pulmonary hypertension in patients with heart failure. J Card Fail 2014;20:650–657.
12. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:e1–82.
13. Report of the WHO/ISFC task force on the definition and classification of cardiomyopathies. Br Heart J 1980;44: 672–673.
14. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211–277.
15. Bard RL, Gillespie BW, Clarke NS, et al. Determining the best ventilatory efficiency measure to predict mortality in patients with heart failure. J Heart Lung Transplant 2006;25:589–595.
16. Leite JJ, Mansur AJ, deFreitas HF, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol 2003;41:2175–2181.
17. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85: 546–562.
18. Wasserman KHJ, Sue DY, Whipp BJ. Principles of Exercise Testing and Interpretation. Philadelphia, Lea & Febiger, 1986, pp.73.
19. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol 1996;27:345–352.
20. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 2011;8:1308–1339.
21. Chua TP, Ponikowski P, Harrington D, et al. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 1997;29:1585–1590.
22. Griffin BP, Shah PK, Ferguson J et al. Incremental prognostic value of exercise hemodynamic variables in chronic congestive heart failure secondary to coronary artery disease or to dilated cardiomyopathy. Am J Cardiol 1991;67:848–853.
23. Myers J, Prakash M, Froelicher V et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
24. Wroblewski H, Kastrup J, Mortensen SA, et al. Abnormal baroreceptor-mediated vasodilation of the peripheral circulation in congestive heart failure secondary to idiopathic dilated cardiomyopathy. Circulation 1993;87(3):849–856.
25. McBride BF, White CM. Anemia management in heart failure: A thick review of thin data. Pharmacotherapy 2004;24:757–767.
26. O'Neill JO, Young JB, Pothier CE, et al. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation 2005;111: 2313–2318.
27. Guazzi M, Myers J, Peberdy MA, et al. Echocardiography with Tissue Doppler Imaging and cardiopulmonary exercise testing in patients with heart failure: A correlative and prognostic analysis. Int J Cardiol 2010;143:323–329.
28. Corra U, Mezzani A, Bosimini E, et al. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. Am Heart J 2002;143:418–426.
29. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of

Intensive Care Medicine (ESICM). Eur Heart J 2008;29: 2388–2442.
30. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119: 1977–2016.
31. Currie PJ, Seward JB, Chan KL, et al. Continuous wave Doppler determination of right ventricular pressure: A simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750–756.
32. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009;179:615–621.
33. Hinderliter AL, Willis PW 4th, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. Circulation 1997;95:1479–1486.
34. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713; quiz 86–88.
35. Dumitrescu D, Oudiz RJ, Karpouzas G, et al. Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. PloS One 2010;5:e14293.

循環器内科学

心不全の予後を予測することはできるのか？

——心不全数式化への挑戦

Is it possible to predict the prognosis of patients with heart failure?
——A challenge to establish a mathematical formula for characterizing heart failure

心不全とは，何らかの構造的あるいは機能的な心臓の異常で心臓のポンプ機能が低下することによって，有効な血液循環が保たれなくなる状態を示す複合的な症候群である[1]．したがって，心不全を引き起こす背景因子や原因は多種多様であり，心不全に至る病態生理も一様ではない．つまり心筋梗塞や狭心症，心臓弁膜症，心筋症などの循環器疾患はもとより，高血圧や糖尿病などの有病率の高い生活習慣病も心不全の原因となることから，それらの終末像である心不全に至る病態を適切かつ効率的に把握し管理することは循環器専門医の重要な命題であるが，心不全が悪性新生物と並び日本の死因の最上位であることから，医療界全体にとっても重要な課題であるといえる．心不全の予後をいまよりも正確に予測することができれば，適切な時期に適切な処置(投薬やデバイスの導入など)を行うことが可能となり，健康寿命の延長や医療経済上の効果に資するものと考えられる．

テーラーメード医療の実現に向けて

心不全の予後，つまり心不全を原因とする死亡や入院に関与するリスクを推定して層別化し介入することは可能なのであろうか．心不全の予後に寄与する因子を推定する数多くの研究がいままで行われ，それらの結果をもとにしたメタ解析によると，いくつかの因子が絞り込まれてきている[2,3]．しかし，これらの因子を用いた予後予測を実臨床に演繹しようとする場合に，背景因子や病態が異なる個々の患者においてかならずしも当てはまるわけではなく，こうした手法の限界がみえてくる．個別医療においては個々の患者の個体間格差が大きく，的確な診断，適切な治療，正確な予後予測を行うに医師のそれまでの経験や裁量，あるいは臨床研究からのエビデンスに頼るところが大きく，画一した方法がないことが問題である．一方，集団医療において明らかにされてきたエビデンスは数理的・平均的であり，診断基準や治療ガイドラインの策定にはおおいに貢献してきた．個別医療と集団医療の利点を十分に活かして有効に活用するためには真に臨床に演繹できるエビデンスが必須であり，これにより個別医療と集団医療をリンクさせた患者個々の病態に即したテーラーメード医療が提供できるものと著者らは考えている(図1)．この考えに基づいて著者らは，個々の患者の状態に即した心不全予後を推定する数式の作成に関する研究を行っている．

心不全の予後を数式で算出することはできるのか？

静止位置からの自由落下運動において，物体の位置(z)は落下開始からの時間(t)と重力加速度(g)とで表され($z=gt^2/2$)，物体の重さや大きさには依存しない．自然科学の一分野である生物学や基礎医学は数理的構造をその学問のなかに内在しているため，その領域において数学的な解を得ることや再現性のある事象を観察することが可能である．この物理学の考えを生物学，医学にも当てはめ，心不全を含めた疾患の進行(Z)も罹患からの時間(T)と疾患構造(G)によって説明できるのではないかと著者らは考えた．しかし，現実世界では物体の大きさや形によってさまざまな空気抵抗を受け，風力などの外的要因によっても物体の位置(z)は影響を受ける．これと同様に，疾患の進行(Z)も多種多様な要因によって影響を受けることは自明であり，また疾患構造(G)も経時的に変化するかもしれ

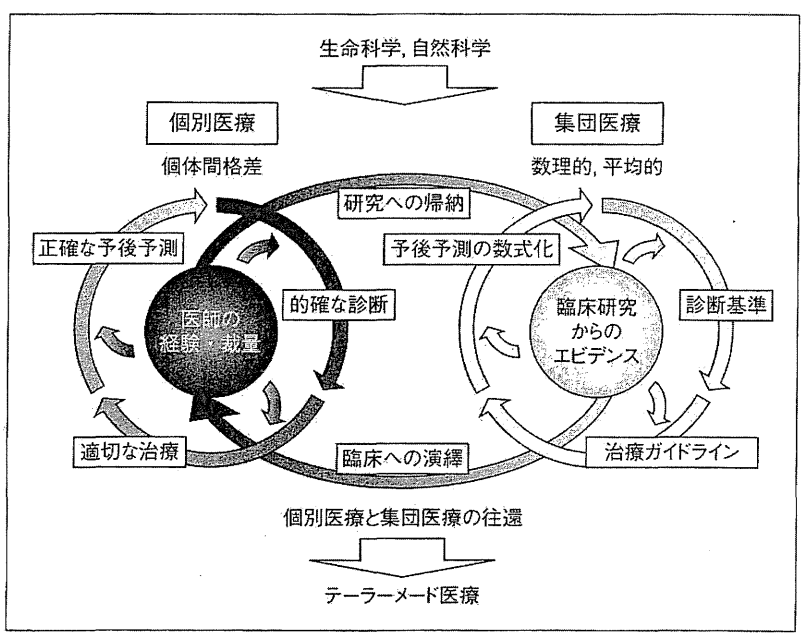

図 1　個別医療と集団医療

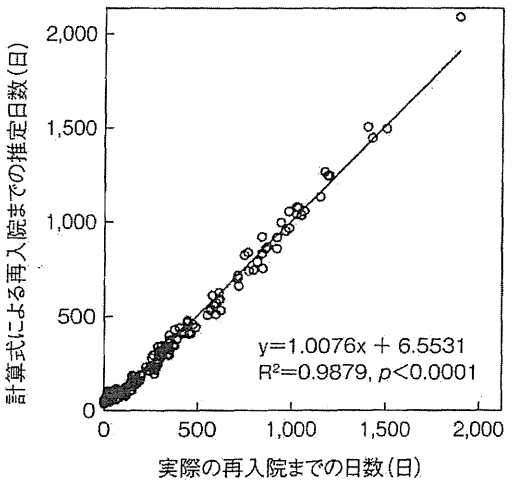

図 2　数式から求めた死亡または心不全による再入院までの推定日数と実測日数[4]

ない．そこで著者らは，心機能のみならず，腎機能，肝機能，消化管機能，不眠，便秘，在宅介護者の有無など他臓器，精神神経状態，社会的要因を加味したさまざまな要因(Xi)と退院後の死亡または心不全による再入院までの日数(Yi)を予測する関数式(Yi=max(T)/βT・{Xi/max(X)}+c)を後向き研究で導き出した．さらに，この関数式から求めた死亡または心不全による再入院までの推定日数は実測日数と非常に近く(図2)，良好な相関を示すことも確認した[4]．現在は本研究成果の妥当性を検証するために前向き観察研究を実施しているところである．

より高精度の心不全予後予測式を作成するために

心不全の予後に関与すると考えられる因子は非常に多岐にわたり，それらのすべてを同定したうえで包含した解析を行うことは事実上不可能である．現在に至るまで心不全予後を予測する多くの研究が行われてきたが，研究ごとに解析対象とする因子は異なり，いままでの臨床経験やそれまでの論文による報告，研究者の直観などによって解析対象とする因子は選択されてきた．そのなかからもっとも関与が高いと考えられる因子を多変量解析で抽出して予後規定因子として報告されている．選択する因子の組合せによっても結果は変化することから，どのような因子の組合せがもっとも適切かという問いに対する答えを出すことは非常に困難である．そこで著者らは，診療録における患者情報，各種検査結果，投薬内容などの膨大な臨床データを集約できるシステムの開発を行い，数学の専門家との共同研究で網羅的に心不全予後に関与する因子の同定を行い，精度の高い心不全予後推定式の作成に取り組んでいるところである．

おわりに

心不全の予後を予測することができるかどうかについては，著者らが算出した式の妥当性を検証する前向き研究の結果をもって判断する必要があると考えている．この研究は数学的構造を生物学や医学のなかに仮定することへの妥当性を心不全という病態を用いて検証しようとする試みであり，いままでにないまったく新しい発想に基づいた挑戦的な研究であると考えている．

謝辞：本研究は大阪大学産業科学研究所知能推進研究分野の鷲尾　隆先生のご協力により行われています．

1) Hunt, S. A.：*J. Am. Coll. Cardiol.*, **46**：e1-e82, 2005.
2) Rahimi, K. et al.：*JACC Heart Fail.*, **2**：440-446, 2014.
3) Ouwerkerk, W. et al.：*JACC Heart Fail.*, **2**：429-436, 2014.
4) Yoshida, A. et al.：*Hypertens. Res.*, **36**：450-456, 2013.

中野　敦，北風政史／Atsushi NAKANO and Masafumi KITAKAZE
国立循環器病研究センター臨床研究部

*　　*　　*

難治性心不全に対する補助循環
――急性期からdestinationまで

Mechanical circulatory support for profound heart failure
――From acute phase to destination therapy including team approach and ethical point of view

中谷武嗣
Takeshi NAKATANI
国立循環器病研究センター移植部門，同臨床栄養部

◎心臓ポンプ機能を機械的に補助する補助循環は，難治性心不全に対して適応が検討される．この補助循環の目的は全身循環の改善・維持をはかるとともに，自己心機能の回復(BTR)，他の補助循環へのつなぎ(BTB)あるいは心臓移植までのつなぎ(BTT)をめざすことである．また心不全が急激に進行する急性心不全においては，補助循環を行うことで今後の治療方針を検討・決定するまで全身循環を維持することが可能となる(BTD)．補助循環を適応することにより時間的猶予を得ることができる("Earn the time")．今後，欧米で行われている心臓移植の適応のない患者に対する長期在宅治療(DT)についても，わが国への導入が検討されている．補助循環を行うことにより，全身循環が良好に維持された状況において，心臓以外の脳を含む諸臓器機能不全などでその治療目的が達成できないと考えられる場合(終末期)には，補助循環の継続について検討することが重要である．

Key word：難治性心不全，補助循環，補助人工心臓，ブリッジ治療，Destination therapy

わが国における補助循環の現状

高度心筋障害による難治性心不全に対しては，心臓ポンプ機能を機械的に補助する補助循環の適応が検討される．この補助循環の目的は，各種の機械的循環補助法により全身循環の改善・維持をはかるとともに，自己心機能の回復(bridge to recovery：BTR)，ほかの補助循環へのつなぎ(bridge to bridge：BTB)，あるいは心臓移植までのつなぎ(bridge to transplantation：BTT)をめざすことである．心不全が急激に進行する急性心不全においては，補助循環を行うことで今後の治療方針を検討・決定するまで全身循環を維持ことが可能となる(bridge to decision：BTD)．

各種の病態による難治性心不全に対し補助循環を適応することにより，時間的猶予を得ることができる("Earn the time")．さらに近年，欧米では心臓移植の適応のない患者に対する長期在宅治療(destination therapy：DT)として多数例に用いられるようになっており，わが国への導入が検討されている[1,2]．

現在わが国で用いられる補助循環としては，①圧補助としての大動脈内バルーンパンピング(IABP)，②流量補助を行う経皮的心肺補助法(PCPS)，③静動脈バイパス(VAB)，および④補助人工心臓(VAS)，がある．使用期間からは，通常数日から1～2週間程度のIABP・PCPS・VAB，1カ月以上施行可能な体外設置型VAS，および長期在宅治療が行える植込型LVASがある[3]．

また，補助循環が用いられる適応病態として，①急性心筋炎や急性心筋梗塞などの急性難治性心不全と，②心筋症による慢性心不全急性増悪など心機能の回復を期待しがたい慢性難治性心不全が