Table 7. ΔSPP Before and After Intervention in Patients With Diabetes Mellitus or End-Stage Renal Disease

	ΔSPP on the Dorsal Side, mmHg	ΔSPP on the Plantar Side, mmHg	P Value	Difference	95% CI
Anterior tibial artery revascularization	14.3±18.0 (direct intervention)	11.8±20.9 (indirect intervention)	0.573	2.57	−4.42 to 9.55
Posterior tibial artery revascularization	13.1±14.1 (indirect intervention)	11.8±9.0 (direct intervention)	0.814	1.33	−10.13 to 12.79

CI indicates confidence interval; and SPP, skin perfusion pressure.

Indeed, Azuma et al[11] reported comparable wound healing with direct versus indirect revascularization after surgical bypass. Catheter-based infrapopliteal intervention studies have also reported no significant differences in the rate of wound healing or limb salvage between direct and indirect revascularization.[12] These differences in published studies could be possibly because of the multifactorial nature of CLI. Indeed, concomitant diabetes mellitus, wound infection, extensive wound size, and other serious comorbidities could have a substantial negative effect on clinical outcomes.[11,12,19] In the clinical setting, the quality of wound management can also influence wound healing, and patient–physician preferences can affect the decision for major amputation. Furthermore, although the toes are frequent sites of tissue loss, some investigators consider them to be in the angiosome of the PTA,[9,20] whereas others contend that the dorsal aspect of the toes belongs to the angiosome of the ATA and the plantar aspect of the toes belongs to the angiosome of the PTA.[10] These conflicting 2D angiosome maps defined by previous investigators may potentially promote a biased diagnosis of direct and indirect revascularization. Thus, objective assessment of the circulation of the foot is necessary to verify the validity of revascularization based on the recently popular concept of the 2D angiosome.

Evaluation of the macrocirculation using measurements of ankle-brachial index and ankle pressure can be falsely elevated because of excessive calcification of the tibial artery[21] and does not reflect blood flow below the ankle. With the limited use of macrocirculation assessment, intense evaluation of the microcirculation is essential in the

Table 9. ΔSPP Before and After Intervention From the Mixed Model With a Random Intercept Adjusting for Autocorrelation

	ΔSPP on Dorsal Side–ΔSPP on Plantar Side, mmHg	Z	P Value	95% CI
Anterior tibial artery revascularization	3.63	1.13	0.257	−2.65 to 9.90
Posterior tibial artery revascularization	−0.87	0.2	0.841	−9.38 to 7.64

CI indicates confidence interval; and SPP, skin perfusion pressure.

setting of CLI.[14–18,22,23] According to recent studies, SPP is a more reliable tool for detecting severe peripheral arterial disease involving calcified vessels and predicting healing of ischemic wounds than other methods for evaluating the macrocirculation and microcirculation (ankle-brachial index, ankle pressure, toe brachial index, toe pressure, and transcutaneous oxygen pressure).[14,17,24] Therefore, this study used SPP to facilitate a detailed assessment of the microcirculation of the dorsal and plantar foot.

The present study found that single tibial artery revascularization results in a significant increase in the microcirculation on both the dorsal and the plantar sides. Furthermore, the dorsal and plantar sides were not significantly different in terms of the amount of change in microcirculation before and after single tibial artery revascularization. Similar findings were observed even in the patients with diabetes mellitus or end-stage renal disease. These comparable effects on foot microcirculation with direct or indirect revascularization strongly support recently published studies showing no clinical difference between direct and indirect revascularization,[11,12] suggesting that the recently defined 2D angiosome theory is less relevant in the treatment of infrapopliteal arterial disease presenting with tissue loss. Furthermore, in the present study, approximately half of the revascularized feet had a demonstrable change in microcirculation that did not correspond to the recently defined 2D angiosome theory. As shown in Figure 3, the effects of tibial revascularization on foot microcirculation might be beyond the interpretation of infrapopliteal angiography. The reasons for this discrepancy between angiographic and hemodynamic findings may be because of (1) the practical perfusion space of the tibial

Table 8. SPP and Ankle-Brachial Index Before and After Intervention From the Mixed Model With a Random Intercept Adjusting for Autocorrelation

	Post–Pre	Z	P Value	95% CI
Anterior tibial artery revascularization				
Dorsal SPP, mmHg	15.2	4.85	<0.001	9.06 to 21.35
Plantar SPP, mmHg	11.1	2.97	0.003	3.78 to 18.42
Ankle-brachial index	0.12	1.84	0.066	−0.08 to 0.26
Posterior tibial artery revascularization				
Dorsal SPP, mmHg	13.13	3.71	<0.001	6.19 to 20.06
Plantar SPP, mmHg	13.25	4.73	<0.001	7.76 to 18.74
Ankle-brachial index	0.17	1.16	0.247	−0.12 to 0.45

CI indicates confidence interval; and SPP, skin perfusion pressure

Table 10. SPP and Ankle-Brachial Index Before and After Intervention in Patients With Diabetes Mellitus or End-Stage Renal Disease From the Mixed Model With a Random Intercept Adjusting for Autocorrelation

	Post–Pre	Z	P Value	95% CI
Anterior tibial artery revascularization				
Dorsal SPP, mmHg	13.08	4.34	<0.001	7.57 to 20.04
Plantar SPP, mmHg	10.87	2.7	0.007	2.99 to 18.76
Ankle-brachial index	0.11	1.49	0.137	−0.03 to 0.25
Posterior tibial artery revascularization				
Dorsal SPP, mmHg	13.11	2.97	0.003	4.45 to 21.77
Plantar SPP, mmHg	11.78	4.15	<0.001	6.22 to 17.34
Ankle-brachial index	0.09	0.45	0.651	−0.31 to 0.49

CI indicates confidence interval; and SPP, skin perfusion pressure.

Table 11. ΔSPP Before and After Intervention in Patients With Diabetes Mellitus or End-Stage Renal Disease From the Mixed Model With a Random Intercept Adjusting for Autocorrelation

	ΔSPP on Dorsal Side–ΔSPP on Plantar Side, mm Hg	Z	P Value	95% CI
Anterior tibial artery revascularization	3.40	0.76	0.450	−4.09 to 9.23
Posterior tibial artery revascularization	5.12	0.19	0.847	−9.05 to 11.03

CI indicates confidence interval; and SPP, skin perfusion pressure.

artery might encompass adjacent angiosomes beyond its immediate borders through branch vessels, choke vessels, and collateral vessels when the other tibial artery is disrupted; (2) severe concomitant disease of more distal arteries, such as the pedal artery, and its branches might hamper the effect of revascularization of the relevant tibial artery (primary source tibial artery); and (3) common anatomic variations in the arteries of the foot may conflict with the application of the 2D angiosome theory.[20,25-31]

Thus, because the definition of the angiosome can be used mistakenly among wound specialists,[32,33] an increasing appreciation of the original concept of angiosome and more recent ideas on the angiosome are crucial to steer the direction of contemporary infrapopliteal revascularization. From a clinical stand point, estimating the autonomous contribution of an individual arterial system to the foot microcirculation before

Table 12. Post-SPP and ΔSPP in Healed and Nonhealed Limbs

|	Healed	Nonhealed	P Value
Overall			
Postdorsal SPP, mm Hg	50.0±18.4	46.8±21.1	0.494
Postplantar SPP, mm Hg	45.9±17.6	42.6±19.1	0.525
ΔSPP on the dorsal side, mm Hg	16.9±16.4	12.6±18.6	0.366
ΔSPP on the plantar side, mm Hg	14.0±17.9	10.4±19.0	0.473
Anterior tibial artery revascularization			
Postdorsal SPP, mm Hg (direct intervention)	49.1±18.7	53.7±20.3	0.463
Postplantar SPP, mm Hg (indirect intervention)	43.0±18.4	47.3±20.8	0.515
ΔSPP on the dorsal side, mm Hg (direct intervention)	16.6±18.7	14.2±19.0	0.693
ΔSPP on the plantar side, mm Hg (indirect intervention)	12.1±19.5	11.6±22.4	0.948
Posterior tibial artery revascularization			
Postdorsal SPP, mm Hg (indirect intervention)	54.6±18.4	33.0±15.8	0.024
Postplantar SPP, mm Hg (direct intervention)	54.6±12.1	33.8±12.3	0.006
ΔSPP on the dorsal side, mm Hg (indirect intervention)	17.9±6.0	9.4±18.4	0.267
ΔSPP on the plantar side, mm Hg (direct intervention)	20.0±10.6	8.0±9.8	0.034

SPP indicates skin perfusion pressure.

Table 13. Post-SPP and ΔSPP in Healed and Nonhealed Limbs From the Mixed Model With a Random Intercept Adjusted for Autocorrelation

	Difference Between Healed and Nonhealed Limbs	Z	P Value	95% CI
Overall				
Postdorsal SPP, mm Hg	4.86	0.87	0.384	−6.08 to 15.79
Postplantar SPP, mm Hg	3.79	0.7	0.486	−6.89 to 14.47
ΔSPP on the dorsal side, mm Hg	4.48	0.93	0.352	−4.96 to 13.92
ΔSPP on the plantar side, mm Hg	3.18	0.6	0.552	−7.30 to 13.66
Anterior tibial artery revascularization				
Postdorsal SPP, mm Hg (direct intervention)	−6.62	−1.02	0.307	−19.33 to 6.09
Postplantar SPP, mm Hg (indirect intervention)	−5.91	−0.85	0.396	−19.56 to 7.73
ΔSPP on the dorsal side, mm Hg (direct intervention)	0.27	0.04	0.968	−12.80 to 13.34
ΔSPP on the plantar side, mm Hg (indirect intervention)	−0.56	−0.07	0.942	−15.64 to 14.51
Posterior tibial artery revascularization				
Postdorsal SPP, mm Hg (indirect intervention)	21.57	2.7	0.007	5.93 to 37.22
Postplantar SPP, mm Hg (direct intervention)	20.82	3.54	0.001	9.28 to 32.36
ΔSPP on the dorsal side, mm Hg (indirect intervention)	8.41	1.24	0.217	−4.94 to 21.76
ΔSPP on the plantar side, mm Hg (direct intervention)	12.00	2.51	0.012	2.62 to 21.38

CI indicates confidence interval; and SPP, skin perfusion pressure.

intervention is an impossible task. Given the findings of this study and the less invasive nature and repeatability of catheter-based endovascular intervention, we still emphasize primary establishment of ≥1 straight-line flow to the foot through revascularization of vessels where it is technically safe and feasible based on angiographic findings. Even the original conception of the 3D angiosome may be an adjunctive concept to explain for inadequate hemodynamic outcome after an initial intervention and may provide some guidance on further treatment strategies.

With respect to wound healing, ≈20 years ago Castronuovo et al[14] reported that SPP>40 mm Hg was highly indicative of tissue loss healing. In this study, SPP>40 mm Hg was observed in not only healed limbs but also nonhealed limbs. Furthermore, post-PTA intervention SPP was significantly higher in healed limbs (>50 mm Hg) than in nonhealed limbs (<40 mm Hg). These findings suggest that revascularization may be only the first step in the process of complete wound healing with the need for further interdisciplinary treatment.

A
Pre   Post

B
Pre   Post
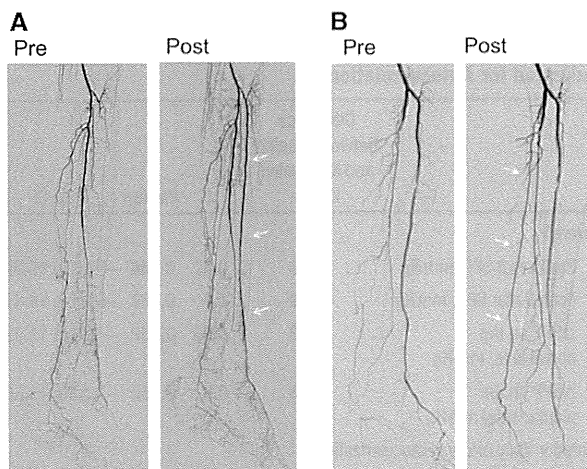
Figure 3. Representative cases with changes in skin perfusion pressure (SPP) not corresponding to the recently defined 2-dimensional angiosome theory. **A,** A case of anterior tibial artery revascularization. SPP (the dorsal side/the plantar side) increased from 34/15 to 42/53 mm Hg after anterior tibial artery revascularization (arrows). Despite a theoretical reperfusion of dorsal side and the remaining plantar artery disease, post-SPP and ΔSPP were higher on the plantar side than on the dorsal side. **B,** A case of posterior tibial artery revascularization. SPP (the dorsal side/the plantar side) increased from 47/40 to 67/52 mm Hg after posterior tibial artery revascularization (arrows). Despite a theoretical reperfusion of plantar side and the patent plantar artery, post-SPP and ΔSPP were higher on the dorsal side than on the plantar side.

Limitations

There are some limitations of this study that should be taken into consideration. First, the present study had a small sample size. Second, the study design was retrospective in nature. Third, there is the possibility that distal embolization of microparticles after endovascular procedures can affect the microcirculation of the foot. Fourth, no procedure outcomes were included because reporting the performance of infrapopliteal interventions was not the intention of this study. Finally, the quality of wound management might not have been uniform.

In conclusion, whether direct intervention or indirect intervention, single tibial artery revascularization involving either the anterior or the posterior tibial artery yielded comparable improvements in the microcirculation of the dorsal and plantar regions of the foot. Approximately half of the feet revascularized had a change in microcirculation that was not consistent with the recently defined 2D angiosome theory. Therefore, the benefits offered by primary angiosome-oriented strategy might be of less paramount importance in the field of infrapopliteal revascularization.

Disclosures

None.

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Effect of Single Tibial Artery Revascularization on Microcirculation in the Setting of Critical Limb Ischemia

Osami Kawarada, Satoshi Yasuda, Kunihiro Nishimura, Shingo Sakamoto, Miyuki Noguchi, Yasuomi Takahi, Koichiro Harada, Masaharu Ishihara and Hisao Ogawa

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Original article

Influence of exercise-induced pulmonary hypertension on exercise capacity in asymptomatic degenerative mitral regurgitation

Kengo Suzuki (MD, PhD)[a,*], Masaki Izumo (MD, PhD)[a], Kihei Yoneyama (MD, PhD)[a], Kei Mizukoshi (MD, PhD)[a], Ryo Kamijima (MD)[a], Seisyou Kou (MD, PhD)[a], Manabu Takai (MD)[a], Keisuke Kida (MD, PhD)[a], Satoshi Watanabe (PT)[b], Kazuto Omiya (MD, PhD, FJCC)[a], Sachihiko Nobuoka (MD, PhD, FJCC)[c], Yoshihiro J. Akashi (MD, PhD, FJCC)[a]

[a] Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan
[b] Department of Rehabilitation Medicine, St. Marianna University Hospital, Kawasaki, Kanagawa, Japan
[c] Department of Laboratory Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

ABSTRACT

Background: Exercise capacity is helpful in the management of patients with mitral regurgitation (MR). However, the determinants of exercise capacity reduction in MR have remained unclear. This study was designed to objectively assess exercise capacity, identify the echocardiographic predictors of exercise capacity, and investigate its impact on development of symptoms in asymptomatic degenerative MR. Methods: A total of 49 consecutive asymptomatic patients (age, 58.9 ± 13.1 years; 82% males) with at least moderate degenerative MR (effective regurgitant orifice area = 0.40 ± 0.14 cm^2; regurgitant volume = 60.9 ± 19.6 mL) underwent the symptom-limited cardiopulmonary exercise testing for assessing exercise capacity (peak oxygen uptake, peak $\dot{V}O_2$; the minute ventilation/carbon dioxide production, $\dot{V}E/\dot{V}CO_2$ slope). All patients also underwent exercise stress echocardiography for detecting exercise-induced pulmonary hypertension (EIPH) defined by systolic pulmonary arterial pressure (SPAP) ≥ 60 mmHg. Results: The mean peak $\dot{V}O_2$ was 22.6 ± 5.1 mL/kg/min ($86.7 \pm 14.1\%$ of age, gender-predicted); peak $\dot{V}O_2$ widely varied (48–121% of predicted), and was markedly reduced (<80.4% of predicted) in 24% of the study patients. The patients with EIPH had lower 2-year symptom-free survival than those without EIPH ($p = 0.003$). The multivariable analysis demonstrated that EIPH was an independent echocardiographic determinant of peak $\dot{V}O_2$ ($p = 0.001$) and $\dot{V}E/\dot{V}CO_2$ slope ($p = 0.021$). Furthermore, the area under curve of age- and gender-adjusted exercise SPAP was 0.88 (95% confidence interval: 0.78–0.97) for reduced exercise capacity. Conclusions: In asymptomatic moderate to severe degenerative MR, EIPH was independently associated with exercise capacity and predicted the occurrence of symptoms. Exercise stress echocardiography is an important tool in managing patients with asymptomatic degenerative MR.

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Introduction

The limitations in exercise and physical activity play a crucial role in the management of patients with mitral regurgitation (MR) [1]. No limitations are clinically observed in asymptomatic

* Corresponding author at: Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan. Tel.: +81 44 977 8111x3313; fax: +81 44 976 7093.
E-mail address: kengo@marianna-u.ac.jp (K. Suzuki).

patients; the subjective assessment does not take the physical activity levels into consideration even though most of those patients are often sedentary. Notable risks are reported in the subsets of asymptomatic patients with MR [2,3]. The guidelines appear to underscore the importance of exercise capacity, and recommend the data assessment of a cardiopulmonary exercise testing (CPX) [1]. CPX measures variables related to cardiorespiratory function, provides noninvasive evaluation of exercise capacity, and allows risk stratification in patients with congestive heart failure [4]. The current American College of Cardiology/American Heart Association [5] and European Society of Cardiology [6] guidelines recommend mitral surgery in asymptomatic patients

with severe MR, preserved left ventricular (LV) function, and pulmonary hypertension (PH) defined by systolic pulmonary arterial pressure (SPAP) >50 mmHg. Likewise, the guidelines advise operating on such patients in the presence of exercise-induced PH (EIPH; SPAP ≥60 mmHg). EIPH may occur even if resting SPAP is in the normal range [7]. Magne et al. have demonstrated that EIPH is associated with reduced symptom-free survival and more accurate than resting PH when predicting the occurrence of symptoms [8]. However, the potential impact of EIPH on exercise capacity has not yet been characterized. This study thus aimed to assess exercise capacity prospectively and objectively and to investigate the influence of EIPH on exercise capacity and symptoms in asymptomatic degenerative MR.

Materials and methods

Study subjects

This prospective study included 65 consecutive asymptomatic patients with degenerative MR, preserved LV systolic function (LV end-systolic diameter <45 mm and LV ejection fraction >60%) [9] and at least moderate MR (effective regurgitant orifice area >0.20 cm^2 or regurgitant volume >30 mL) referred for exercise stress echocardiography between October 2011 and April 2013. The cardiologists interviewed the study patients and recorded past medical history. An asymptomatic patient was defined as a patient who has no specific symptoms of heart failure, such as shortness of breath, angina, dizziness, or syncope with exertion. The systematic interview and physical examination were performed by experienced cardiologists and symptomatic status was carefully assessed. Of these, patients with a history of congestive heart failure or SPAP ≥50 mmHg at rest based on the previous echocardiographic assessment ($n = 3$), concomitant valvular stenosis or regurgitation ($n = 3$), atrial fibrillation ($n = 4$), inability to exercise ($n = 3$), and the absence of measurable SPAP during exercise ($n = 3$) were excluded from this study; finally, 49 patients were enrolled.

Conventional and exercise echocardiography

Echocardiography was performed in the left lateral decubitus position using a commercially available system (Vivid E9, General Electric-Vingmed, Milwaukee, WI, USA). Images were obtained with a 3.5-MHz transducer in the parasternal and apical views. The ratio of early (E) to late (A) transmitral velocities (E/A) and deceleration time of E velocity were obtained using pulsed wave Doppler in the apical four-chamber view. E' was measured at the septal mitral annulus in the apical four-chamber view. The E/E' ratio was measured to estimate LV filling pressure [10]. The severity of MR was measured with the Doppler volumetric method [11].

All patients underwent a symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table (Ergometer & tilt Table 750EC, Lode, Groningen, Netherlands) for continuous 2D echocardiography. After a 3-min workload at 25 watt (W), the intensity was increased by 25 W every 3 min. The obtained data were digitally stored. Electrocardiograms, blood pressure, and heart rate were recorded at each stage. According to the guidelines [5], EIPH was defined as SPAP ≥60 mmHg during exercise.

CPX

All patients underwent CPX on a sitting cycle ergometer (Accura, Mitsubishi Electrical Engineering Co., Tokyo, Japan) on different days within 2 weeks before or after exercise echocardiography. After 3-min rest and 4-min warm-up at 20 W, exercise load intensity was gradually and linearly increased by 1 W or 2 W per 6 s. The expired gas analysis was performed continuously throughout the CPX on a breath-by-breath basis with an AE-300 cart (Minato Medical Science, Osaka, Japan). Anaerobic threshold (AT), peak oxygen uptake (peak $\dot{V}O_2$), and the ventilator equivalent to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$) slope were obtained from the results of CPX. Peak $\dot{V}O_2$ was expressed as absolute peak $\dot{V}O_2$ or normalized peak $\dot{V}O_2$ (percent of age and gender predicted) [12].

Symptom-free survival

Patient follow-up was performed according to the current guidelines. Patients were classified as symptomatic when shortness of breath, angina, dizziness, or syncope with exertion was identified during the follow-up. Experienced cardiologists performed the physical examination and echocardiography and carefully assessed symptomatic status. Patients were reevaluated every 6 months, including physical examinations and echocardiography. The intervals of evaluations were shortened to 3 months in patients who revealed changes compared with the previous measurements or if echocardiographic measurements were close to the guideline cut-off values used for surgical indication. At the end of this study, physicians arranged telephone interviews with patients with the final follow-up at >6 months and reevaluated obtained information. To ensure blinding and to avoid influencing the physician's decision with exercise echocardiography and cardiopulmonary exercise testing results, the data on exercise capacity, SPAP, and the occurrence of EIPH were not sent to the referral physician.

Ethics

This study was performed in accordance with the ethical principles set forth in the Declaration of Helsinki; the study protocol was approved by the St. Marianna University School of Medicine Institutional Committee on Human Research (No. 1288) in Kanagawa, Japan. Written informed consent was obtained from all patients prior to their enrollment.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as percent. The unpaired Student's t test and χ^2 test were used to compare variables between the following two groups, the low exercise capacity group and maintained exercise capacity group determined by first quartile of predicted peak $\dot{V}O_2$ (80.4%). The associations between exercise SPAP versus peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope were investigated using the Pearson correlation. Multiple linear regression analysis was performed to evaluate the association of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope with clinical and echocardiographic parameters at rest and peak exercise. Multivariable linear regression analysis was used to determine the associations of peak $\dot{V}O_2$ with age, gender, resting LV end-systolic volume index, E', regurgitant volume, and EIPH, respectively. Probabilities of symptom-free survival were obtained by using the Kaplan–Meier estimates according to the presence of exercise intolerance or exercise PH and then compared by using the two-sided log-rank test. Statistical significance was set at $p < 0.05$. The statistical analysis was performed with commercially available software (SPSS-18.0 software, SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics and echocardiographic parameters

The baseline characteristics are shown in Table 1 according to the exercise capacity; 12 patients were stratified into the low

Table 1
Baseline characteristics.

	Overall (n = 49)	Low exercise capacity (n = 12, 24%)	Maintained exercise capacity (n = 37, 76%)	p-Value
Clinical data				
Age (years)	58.9 ± 13.1	67.3 ± 11.6	56.2 ± 12.6	<0.0001
Gender male, n (%)	40 (82)	6 (50)	34 (92)	0.001
BMI (kg/m²)	22.6 ± 2.9	22.7 ± 2.7	22.5 ± 3.0	0.845
Rest SBP (mmHg)	137.3 ± 18.4	145.5 ± 21.8	134.0 ± 16.2	0.247
Rest DBP (mmHg)	77.9 ± 10.6	78.6 ± 12.2	77.6 ± 10.1	0.797
Rest HR (beat/min)	76.9 ± 10.6	77.3 ± 12.8	68.7 ± 11.7	0.847
Peak exercise SBP (mmHg)	178.3 ± 25.1	188.2 ± 26.4	171.4 ± 23.4	0.028
Peak exercise DBP (mmHg)	79.9 ± 14.8	81.4 ± 16.8	79.4 ± 14.4	0.691
Peak exercise HR (beat/min)	142.0 ± 14.2	137.3 ± 16.4	144.1 ± 13.4	0.179
Log BNP (pg/mL)	1.5 ± 0.4	1.8 ± 0.5	1.5 ± 0.3	0.017
CPX				
AT (mL/min/kg)	15.3 ± 3.2	11.6 ± 2.6	16.4 ± 2.6	<0.0001
Peak $\dot{V}O_2$ (mL/min/kg)	22.6 ± 5.1	16.1 ± 3.0	24.5 ± 3.8	<0.0001
% predicted peak $\dot{V}O_2$	86.7 ± 14.1	66.9 ± 3.0	92.7 ± 8.7	<0.0001
$\dot{V}E/\dot{V}CO_2$ slope	29.1 ± 4.5	33.7 ± 4.7	27.7 ± 3.4	<0.0001
Etiology of MR, n (%)				
AML prolapse	9 (18)	2 (17)	7 (19)	0.861
PML prolapse	36 (74)	8 (67)	28 (76)	0.539
Both leaflets prolapse	1 (2)	0 (0)	1 (3)	0.565
Sclerotic change	3 (6)	2 (17)	1 (3)	0.080

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BNP, brain natriuretic peptide; CPX, cardiopulmonary exercise testing; AT, aerobic threshold; $\dot{V}O_2$, oxygen uptake; VE, ventilatory equivalent; $\dot{V}CO_2$, carbon dioxide output; MR, mitral regurgitation; AML, anterior mitral leaflet; PML, posterior mitral leaflet.

exercise capacity group and 37 patients into the maintained exercise capacity group. Of the study patients, 82% were male, 57% received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 8% received beta-blockers, 22% received calcium blockers, and 27% received diuretics. The mean peak $\dot{V}O_2$ widely varied (48–121% of predicted) and was markedly reduced (<80.4% of predicted) in 24% of the study population. Significant differences in age, gender, and log brain natriuretic peptide (BNP) were found

Table 2
Resting and exercise echocardiographic data.

	Overall (n = 49)	Low exercise capacity (n = 12, 24%)	Maintained exercise capacity (n = 37, 76%)	p-Value
Resting				
LAVI (mL/m²)	53.4 ± 16.0	54.4 ± 15.5	53.1 ± 16.4	0.807
IVST (mm)	8.7 ± 1.2	8.9 ± 1.4	8.6 ± 1.1	0.424
PWT (mm)	8.6 ± 1.1	8.6 ± 1.0	8.5 ± 1.1	0.907
LVDd (mm)	54.7 ± 5.9	53.2 ± 5.1	55.1 ± 6.1	0.320
LVDs (mm)	32.2 ± 4.9	31.3 ± 5.6	32.5 ± 4.6	0.460
LVEDVI (mL/m²)	81.3 ± 16.7	77.0 ± 12.6	82.7 ± 17.8	0.311
LVESVI (mL/m²)	27.8 ± 7.9	25.2 ± 10.6	28.7 ± 6.7	0.190
LVEF (%)	66.7 ± 6.7	67.8 ± 10.1	66.4 ± 5.3	0.547
E/A	1.6 ± 0.6	1.4 ± 0.6	1.7 ± 0.6	0.150
E'	8.2 ± 2.3	7.1 ± 2.1	8.5 ± 2.3	0.064
E/E'	14.0 ± 5.1	15.7 ± 6.7	13.4 ± 4.5	0.156
ERO (cm²)	0.40 ± 0.14	0.35 ± 0.13	0.41 ± 0.14	0.171
RV (mL)	60.9 ± 19.6	53.4 ± 19.1	63.4 ± 19.3	0.127
SPAP (mmHg)	29.7 ± 6.9	30.9 ± 7.9	29.3 ± 6.6	0.478
Exercise				
LAVI (mL/m²)	48.3 ± 17.3	46.9 ± 15.3	48.8 ± 18.1	0.749
IVST (mm)	8.8 ± 1.2	8.9 ± 1.2	8.8 ± 1.2	0.816
PWT (mm)	8.7 ± 1.0	8.7 ± 1.0	8.7 ± 1.2	0.866
LVDd (mm)	54.5 ± 6.1	51.8 ± 5.6	55.4 ± 6.1	0.081
LVDs (mm)	30.9 ± 5.6	29.2 ± 6.3	31.4 ± 5.3	0.225
LVEDVI (mL/m²)	85.9 ± 17.3	83.7 ± 12.8	86.7 ± 18.6	0.605
LVESVI (mL/m²)	26.0 ± 7.8	26.9 ± 12.6	25.7 ± 5.7	0.628
LVEF (%)	70.0 ± 7.0	68.5 ± 10.4	70.5 ± 5.6	0.399
E/A	1.4 ± 0.5	1.4 ± 0.4	1.4 ± 0.6	0.857
E'	12.5 ± 4.8	10.7 ± 3.8	13.1 ± 5.1	0.090
E/E'	13.0 ± 6.1	14.0 ± 6.2	12.8 ± 6.1	0.459
SPAP (mmHg)	47.5 ± 12.4	55.8 ± 10.3	44.9 ± 11.9	0.007
EIPH, n (%)	9 (27)	5 (42)	4 (11)	0.029

LAVI, left atrial volume index; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; E/A, the ratio of early diastolic (E) and late diastolic (A) transmitral flow velocities; Dct, deceleration time of E wave velocity; E/E', the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity (E'); ERO, effective regurgitant orifice; RV, regurgitant volume; SPAP systolic pulmonary arterial pressure; EIPH, exercise-induced pulmonary hypertension.

between the low exercise capacity and maintained exercise capacity groups. The patients in the low exercise capacity were older, several of them female; these patients revealed higher BNP than the patients in the maintained exercise capacity. The patients with low exercise capacity had greater $\dot{V}E/\dot{V}CO_2$ slope than those with maintained exercise capacity. The ratio of patients who stopped exercise because of dyspnea was greater in the low exercise capacity group (75%, $n = 9$) than in the maintained exercise capacity group (41%, $n = 15$, $p < 0.0001$). Systolic blood pressure increased from 137 ± 18 mmHg at rest to 178 ± 25 mmHg at peak exercise (paired $p < 0.0001$). Systolic blood pressure at peak exercise in the low exercise capacity group (188 ± 26 mmHg) was higher than the maintained exercise capacity group (171 ± 23 mmHg, $p = 0.028$). The heart rate increased from 77 ± 11 bpm at rest to 142 ± 14 bpm at peak exercise (paired $p < 0.0001$). The heart rates at peak exercise were similar between the low exercise capacity (137 ± 16 bpm) and the maintained exercise capacity (144 ± 13 bpm, $p = 0.179$) groups.

The exercise echocardiographic data at rest and during exercise are shown in Table 2. The conventional echocardiographic parameters did not differ between the two groups. Of note, no significant differences in the severity of MR or mitral leaflet prolapse localization were found between the two groups.

Changes in SPAP at rest and exercise

Significant changes in resting and exercise SPAP were found both in the low exercise capacity and maintained exercise capacity groups (Table 2). There were no significant differences in resting SPAP, whereas exercise SPAP was greater in the low exercise capacity group than the maintained exercise capacity group (Fig. 1). Of the study patients, 27% asymptomatic patients with moderate or severe degenerative MR developed EIPH; the prevalence of EIPH was greater in the low exercise capacity than maintained exercise capacity groups.

Relationship between echocardiographic predictors and exercise capacity

At rest, peak $\dot{V}O_2$ was correlated with the LV end-systolic volume index, E/A, E', and E/E', respectively. Resting MR severity or
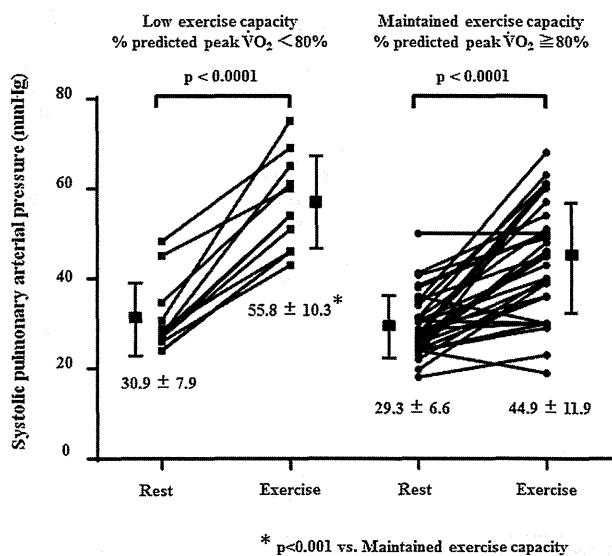
SPAP was not associated with exercise capacity (Table 3). However, exercise SPAP was negatively correlated with peak $\dot{V}O_2$ ($r = -0.619$, $p = 0.001$) and positively correlated with $\dot{V}E/\dot{V}CO_2$ slope ($r = 0.406$, $p = 0.007$; Fig. 2). In the multivariable linear regression analysis, age, gender, E', and EIPH were independent determinants of peak $\dot{V}O_2$ ($p = 0.001$). Furthermore, age, and EIPH were independent determinants of $\dot{V}E/\dot{V}CO_2$ slope ($p = 0.021$; Table 4).

Receiver operating characteristic curve based on rest and exercise SPAP for reduced exercise capacity

The receiver operating characteristic analysis was performed for predicting reduced exercise capacity on a basis of rest and exercise SPAP. Resting SPAP was not significant, whereas, the area under the curve for exercise SPAP was 0.76 (95% confidence interval: 0.62–0.90) for reduced exercise capacity. Exercise SPAP ≥50.9 mmHg predicted reduced exercise capacity with a sensitivity of 67% and a specificity of 76%. Furthermore, the area under curve of age- and gender-adjusted exercise SPAP was 0.88 (95% confidence interval: 0.78–0.97) for reduced exercise capacity (Fig. 3).

Symptom-free survival

Follow-up data collection was complete in 49 patients (100%) with a mean follow-up of 21.7 ± 7.4 months (range, 2–25 months). During the follow-up period, 40 patients (82%) remained asymptomatic and 9 patients (18%) developed symptoms (6.8 ± 5.1 months).

Table 3
Correlations with peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope.

Variables	Correlation with peak $\dot{V}O_2$		Correlation with $\dot{V}E/\dot{V}CO_2$ slope	
	r	p-Value	r	p-Value
Age (years)	−0.690	<0.0001	0.618	<0.0001
Log BNP (pg/mL)	−0.510	<0.0001	0.512	<0.0001
Resting				
HR (beat/min)	−0.127	0.511	0.092	0.634
Systolic BP (mmHg)	−0.166	0.390	0.277	0.145
Diastolic BP (mmHg)	0.129	0.506	0.044	0.819
LVEDVI (mL/m²)	0.273	0.076	−0.145	0.354
LVESVI (mL/m²)	0.441	0.003	−0.250	0.105
LVEF (%)	−0.252	0.103	0.210	0.094
E/A ratio	0.325	0.033	−0.397	0.008
E'	0.443	0.003	−0.464	0.002
E/E'	−0.336	0.028	0.328	0.032
LAVI (mL/m²)	−0.104	0.505	−0.055	0.728
ERO (cm²)	0.180	0.248	−0.143	0.359
RV (mL)	0.204	0.188	−0.089	0.570
SPAP (mmHg)	−0.031	0.842	0.016	0.919
Exercise				
HR (beat/min)	0.127	0.511	−0.339	0.072
Systolic BP (mmHg)	−0.008	0.958	0.102	0.520
Diastolic BP (mmHg)	−0.301	0.052	0.267	0.097
LVEDVI (mL/m²)	0.239	0.123	−0.113	0.471
LVESVI (mL/m²)	0.307	0.045	−0.256	0.097
LVEF (%)	−0.139	0.375	0.225	0.147
E/A ratio	0.104	0.559	−0.214	0.224
E'	0.306	0.049	−0.405	0.008
E/E'	−0.158	0.371	0.200	0.245
LAVI (mL/m²)	−0.004	0.979	0.055	0.728
SPAP (mmHg)	−0.619	<0.0001	0.406	0.007

$\dot{V}O_2$, oxygen uptake; $\dot{V}E$, ventilatory equivalent; $\dot{V}CO_2$, carbon dioxide output; BNP, brain natriuretic peptide; HR, heart rate; BP, blood pressure; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; E/A, the ratio of early diastolic (E) and late diastolic (A) transmitral flow velocities; Dct, deceleration time of E wave velocity; E/E', the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity (E'); LAVI, left atrial volume index; ERO, effective regurgitant orifice; RV, regurgitant volume; SPAP, systolic pulmonary arterial pressure.
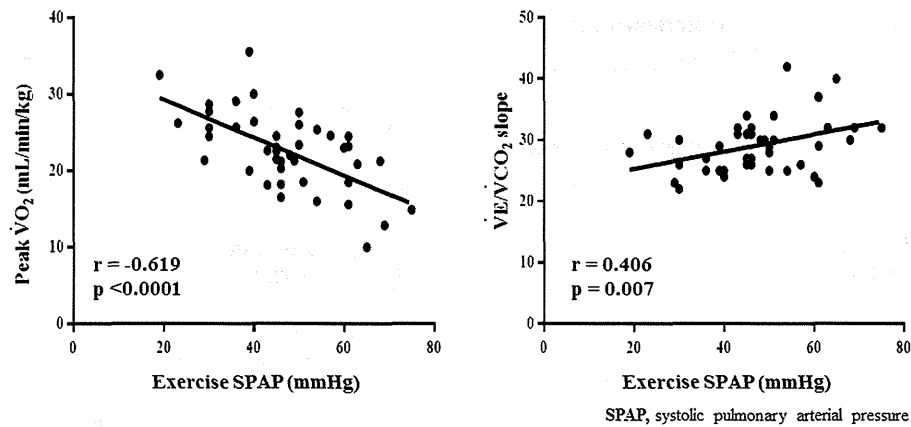

Low exercise capacity
% predicted peak $\dot{V}O_2$ <80%

Maintained exercise capacity
% predicted peak $\dot{V}O_2$ ≥80%

$p < 0.0001$ $p < 0.0001$

55.8 ± 10.3*

30.9 ± 7.9

29.3 ± 6.6   44.9 ± 11.9

Rest   Exercise   Rest   Exercise

* $p < 0.001$ vs. Maintained exercise capacity

Fig. 1. Changes in systolic pulmonary arterial pressure (SPAP) at rest and during exercise in each group. No significant difference in resting SPAP was found between the low and maintained exercise capacity groups. However, significant difference in exercise SPAP was found between the two groups. $\dot{V}O_2$, peak oxygen uptake.

Fig. 2. Relationship between exercise systolic pulmonary arterial pressure (SPAP) and exercise capacity. A correlation was found between exercise SPAP versus peak oxygen uptake ($\dot{V}O_2$; r = −0.619, p = 0.001) and the minute ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope (r = 0.406, p = 0.007), respectively.

Table 4
Multivariate linear regression; predictors of peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope.

Variables	Peak $\dot{V}O_2$			$\dot{V}E/\dot{V}CO_2$ slope		
	Coefficient	95% CI	p-Value	Coefficient	95% CI	p-Value
Age	−0.266	−0.356 to −0.175	<0.0001	0.186	0.098 to 0.274	<0.0001
Gender	4.740	2.494 to 6.985	0.001	−2.350	−5.048 to 0.349	0.086
LVESVI	0.118	−0.097 to 0.334	0.274	0.118	−0.097 to 0.334	0.274
E'	−0.635	−1.162 to −0.108	0.020	0.043	−0.594 to 0.681	0.891
RV	0.014	−0.049 to 0.077	0.658	0.014	−0.049 to 0.077	0.658
EIPH	−3.628	−5.649 to 1.608	0.001	2.778	0.440 to 5.115	0.021

$\dot{V}O_2$, oxygen uptake; $\dot{V}E$, ventilatory equivalent; $\dot{V}CO_2$, carbon dioxide output; LVESVI, left ventricular end-systolic volume index; E', early diastolic mitral annular velocity; RV, regurgitant volume; EIPH, exercise-induced pulmonary hypertension.
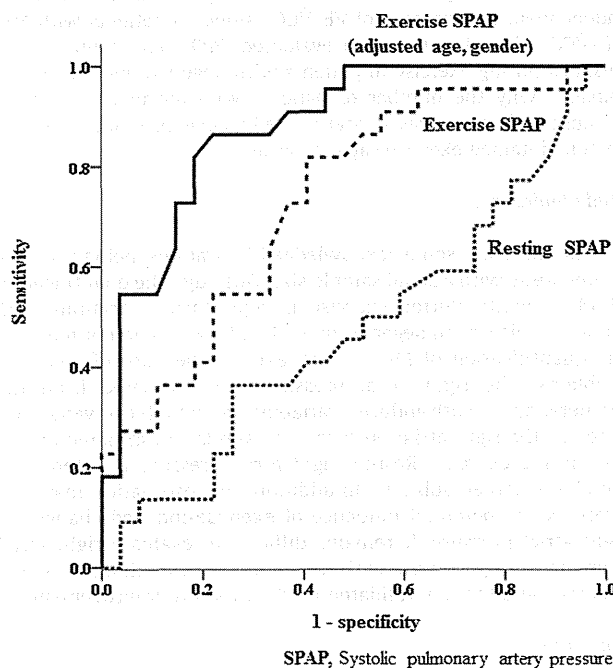

Fig. 3. Receiver operating characteristic curve based on rest and exercise systolic pulmonary arterial pressure (SPAP) for reduced exercise capacity. The area under curve by exercise SPAP was 0.76 (95% confidence interval: 0.62–0.90) for reduced exercise capacity. Exercise SPAP ≥50.9 mmHg predicted peak oxygen uptake ≤80.4% with a sensitivity of 67% and a specificity of 76%. Furthermore, the area under curve by exercise SPAP adjusted age gender was 0.88 (95% confidence interval: 0.78–0.97) for reduced exercise capacity.

The patients with low exercise capacity had lower symptom-free survival than those with maintained exercise capacity (p = 0.001, Fig. 4A). Whereas, the patients with EIPH had lower 2-year symptom-free survival than the patients without EIPH (p = 0.003, Fig. 4B).

Discussion

The results of this study demonstrated that (1) approximately 1/4 of asymptomatic patients with moderate to severe degenerative MR had reduced exercise capacity; (2) exercise SPAP was more accurate than resting SPAP for predicting exercise capacity; (3) EIPH was an independent echocardiographic predictor of exercise capacity; and (4) EIPH was associated with reduced symptom-free survival.

In general, the assessment of exercise capacity in MR is based on symptoms occurring with exertion [1]. Asymptomatic patients with severe MR tend to incur notable mortality under conservative management [2,3,13] because of the underestimated disease severity. One study has demonstrated that exercise capacity widely ranges from supernormal to markedly reduced in asymptomatic patients with degenerative MR and approximately 1 out of 4–5 patients reveals unexpected and remarkably reduced exercise capacity [14]. We also confirmed that exercise capacity was markedly reduced in 24% of asymptomatic patients with degenerative MR. Accordingly, the guidelines underscore the importance of exercise capacity and recommend patients with degenerative MR to undergo an exercise testing for objective assessment [1].

Although some patients with severe MR complain of no functional limitations, others with similar MR develop severe functional limitations [2,3,13]. The determinants of exercise capacity reduction in MR have remained unclear with no definite associations between peak $\dot{V}O_2$ and MR [15]. Generally, exercise

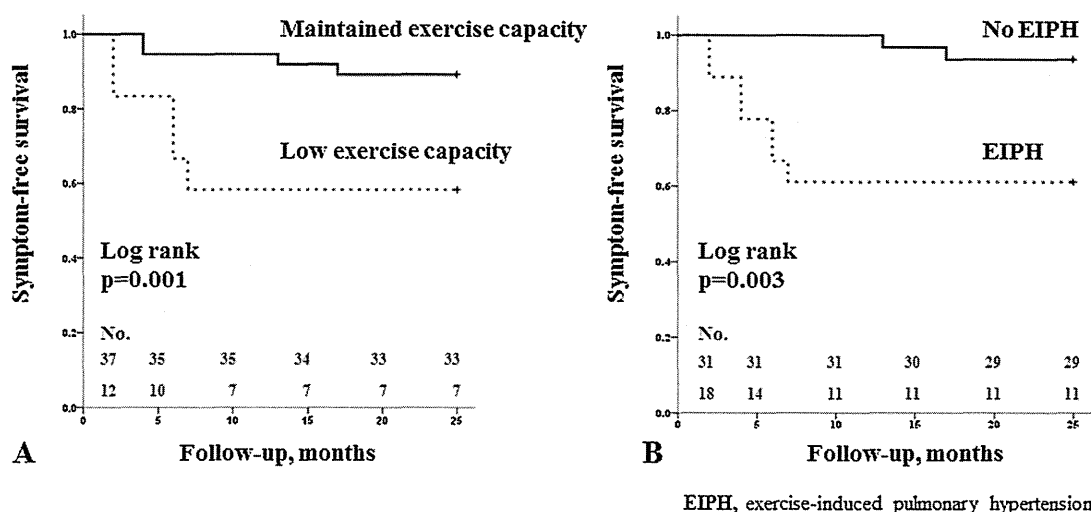6   K. Suzuki et al./Journal of Cardiology xxx (2014) xxx–xxx

Fig. 4. Symptom-free survival according to exercise capacity. The patients with low exercise capacity had lower symptom-free survival than those with maintained exercise capacity ($p = 0.001$) (A), whereas the patients with exercise-induced pulmonary hypertension (EIPH) had lower 2-year symptom-free survival than those without EIPH ($p = 0.003$) (B).

capacity is affected by LV characteristics; particularly, diastolic function is a major exercise capacity determinant [16–18] as it is shown by its strong influence on exercise capacity in degenerative MR [19]. The impact of diastolic dysfunction on exercise capacity is also supported by the univariate association between peak $\dot{V}O_2$ and deceleration time, a marker of LV compliance [14]. In the present study, we also demonstrated that peak $\dot{V}O_2$ was correlated with diastolic function indices.

Patients with valvular heart disease are usually classified hemodynamically as having pressure or volume overload [20–22]. MR is classified as a volume overload state. Increases in LV filling and left atrial pressure due to hemodynamics overload of MR induce significant rises in pulmonary venous, capillary, and arterial pressures. This additional pressure load imposed on the right heart and pulmonary circulation triggers PH which often remarkably worsens during exercise. Hasuda et al. [23] examined the determinant factors for exercise capacity in patients with regurgitant valvular heart disease. They demonstrated that the patients with a plateau in $\dot{V}O_2$ at peak exercise had higher pulmonary arterial pressure than those without a plateau in $\dot{V}O_2$. They concluded that exercise capacity in patients with regurgitant valvular heart disease was limited by the magnitude of PH during exercise. Butler et al. [24] reported that PH contributed to exercise capacity in heart failure by impairing the cardiac output response to exercise. The development of PH during exercise probably limits the increment in cardiac output, resulting in the appearance of a plateau in $\dot{V}O_2$. Moderate to severe MR limits incremental increases in cardiac output during exercise. In addition, reduced baseline forward stroke volume demonstrated by lower peak O_2 pulse independently predicts reduced exercise capacity, probably through inability to sustain large forward stroke volume due to MR [14].

Since $\dot{V}E/\dot{V}CO_2$ slope increases with the severity of heart failure and the level of dead space ventilation, it has been regarded as a useful index for dyspnea during exercise [25] and a strong predictor of mortality in patients with chronic heart failure [26]. Peak $\dot{V}O_2$ is confounded by its dependence on subject effort, which is not the case for the $\dot{V}E/\dot{V}CO_2$ slope. Earlier research in patients with chronic heart failure has demonstrated a significant relationship between the $\dot{V}E/\dot{V}CO_2$ slope and PH [27]. The resultant increase in pulmonary vascular resistance, as seen in PH, leads to an increase in physiologic dead space secondary to ventilation–perfusion mismatch. Falling arterial oxygen saturations lead to earlier development of lactic acidosis which, combined with decreased mixed venous oxygen content and other neural signals, triggers an exaggerated ventilatory response resulting in an elevation of the $\dot{V}E/\dot{V}CO_2$ slope during progressive exercise [28–30]. Therefore $\dot{V}E/\dot{V}CO_2$ slope allows noninvasive measurements of disease severity that are effort independent. In the present study, we demonstrated that exercise SPAP was positively correlated with $\dot{V}E/\dot{V}CO_2$ slope and EIPH was an independent determinant of $\dot{V}E/\dot{V}CO_2$ slope. In patients with MR, $\dot{V}E/\dot{V}CO_2$ slope has not been evaluated. EIPH may contribute to dyspnea during exercise in patients with degenerative MR, which explains why the number of patients who terminated exercise because of dyspnea was greater in the low exercise capacity group than maintained exercise capacity group.

Study limitations

Our study has some acknowledged limitations, being a single-center study with a small sample size. Although the quantification of MR severity during exercise is reproducible, accurate, and clinically relevant in degenerative MR [31], we could not measure the quantification of MR at peak exercise because of technical problems. The right atrial pressure was estimated from the diameter and breath-induced variability of the inferior vena cava, whereas the right atrial pressure was similarly estimated at rest and during exercise. Resting right atrial pressure is extensively variable between subjects. In addition, this estimation may also overlook the potential influence of exercise-induced changes in right atrial pressure. It remains difficult to evaluate right atrial pressure during exercise with the noninvasive method; thus, low accuracy and the not-validated method require improvement.

Conclusions

In asymptomatic patients with moderate to severe degenerative MR, exercise capacity varied widely and markedly decreased in 1/4 of the study patients. EIPH was the independent echocardiographic determinant of reduced exercise capacity. Furthermore, EIPH was associated with reduced symptom-free survival.

Conflict of interest

None declared.

Acknowledgments

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ORIGINAL ARTICLE

Early defects identified by computed tomography angiography are associated with left ventricular dysfunction and exercise intolerance following acute myocardial infarction

Ken Kongoji · Kihei Yoneyama · Kohei Koyama · Takanobu Mitarai ·
Ryo Kamijima · Keisuke Kida · Yasuyuki Kobayashi · Kazuto Omiya ·
Yoshihiro J. Akashi

Abstract

Purpose We evaluated the influence of early defects (EDs) in the infarcted myocardium after reperfusion, detected by computed tomography angiography (CTA), on cardiac function and exercise capacity in the chronic phase.
Materials and methods We retrospectively analyzed 48 acute myocardial infarction (AMI) patients who underwent both CTA using 64-slice multidetector CT within 14 ± 6 days and cardiopulmonary exercise testing within 3 months after AMI onset between 2005 and 2007. The patients were divided into 2 groups: the EDs <75 % or EDs ≥75 % group. Brain natriuretic peptide (BNP) levels and ejection fraction (EF) were measured 6 months after AMI onset.
Results The minute ventilation–carbon dioxide production slope was significantly higher in the EDs ≥75 % group (28.7 ± 4.9) than in the EDs <75 % group (25.1 ± 3.1, $P = 0.048$). EF at 6 months was significantly lower in the EDs ≥75 % group (48.1 ± 12.0 %) than in the EDs <75 % group (56.8 ± 10.0 %, $P = 0.01$). Log of BNP levels was higher in the EDs ≥75 % group than in the EDs <75 % group ($P < 0.001$).
Conclusion EDs detected by CTA in the acute phase of AMI influenced myocardial dysfunction and exercise intolerance in the chronic phase.

K. Kongoji · K. Yoneyama · K. Koyama · T. Mitarai ·
R. Kamijima · K. Kida · K. Omiya · Y. J. Akashi (✉)
Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
e-mail: yoakashi-circ@umin.ac.jp

Y. Kobayashi
Department of Radiology, St. Marianna University School of Medicine, Kawasaki, Japan

Introduction

The significance of early myocardial reperfusion on the prognosis is well known in patients with acute myocardial infarction (AMI) [1]. Recovery of cardiac systolic function becomes more favorable if the infarcted area is very small. In recent years, coronary computed tomography angiography (CTA) has become a standard approach for noninvasive assessment of coronary arteries [2–6]. The use of CTA to assess cardiac morphology and myocardial perfusion has been the subject of ongoing studies because of recent technical developments [3, 7–9]. It has been reported that CTA findings for early defects (EDs) in myocardial perfusion in the left ventricle were consistent with findings of enhanced perfusion magnetic resonance imaging (MRI) in pig models of AMI [10]. In humans, EDs on CTA are often observed in the early phase following contrast bolus injection in patients with AMI [11–14]. One study reported that Q-wave infarction and segment wall motion abnormalities were more frequently observed in patients with EDs than in those without EDs [12]. These results suggest that EDs on CTA should indicate the cardiac abnormalities associated with myocardial infarction.

On the other hand, exercise capacity and activity status are important factors for patients with AMI after hospitalization because these factors are well-established predictors of cardiovascular overall mortality [7, 15, 16]. In one study involving 296 AMI patients after rehabilitation, patients with large myocardial infarctions measured by peak creatine phosphokinase levels had lower peak oxygen

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uptake (VO_2) than did those with less extensive infarction [17]. Thus, assessment of myocardial viability using CTA should provide additional clinical and imaging information on the extent and location of infarction in the chronic phase. However, the association of myocardial EDs on CTA with exercise capacity in patients with AMI has not been fully evaluated.

Therefore, this study aimed to evaluate the influence of EDs in infarcted myocardium after reperfusion detected by CTA on cardiac function and exercise capacity in the chronic phase.

Materials and methods

Subjects

Of the AMI patients treated with emergent percutaneous coronary intervention (PCI) within 12 h of AMI onset between May 2005 and August 2007, this retrospective study included 48 patients with de novo AMI (35 males, 13 females) who underwent coronary CTA using 64-slice multidetector computed tomography within 14 ± 6 days after AMI onset. Upon arrival at the emergency department, venous blood samples were collected from the cubital vein. The cardiologists diagnosed AMI on the basis of electrocardiography (ECG) changes, echocardiographic findings, immunochromatographic detection of human heart fatty acid-binding protein in blood serum, and hematological findings, including blood levels of creatine kinase-MB (CK-MB). The PCI procedure was considered successful when residual stenosis was <25 % and thrombosis in myocardial infarction (TIMI) grade-3 flow was established. Blood samples were collected every 3 h after PCI to determine the peak levels of cardiac enzymes. All patients were treated with conventional medications after PCI. Patients with previous left main trunk lesions, cardiogenic shock, cardiomyopathy, atrial fibrillation, active infectious disease, hematological disease, and end-stage renal and hepatic disease were excluded (Fig. 1). Six months after AMI onset, brain natriuretic peptide (BNP) levels and left ventricular ejection fraction (LVEF) were also measured. Of the 48 study patients, 26 underwent cardiopulmonary exercise test (CPX) 3 months after AMI onset.

Percutaneous coronary intervention and TIMI grade

All patients underwent invasive coronary angiography using the standard techniques immediately after the primary PCI was performed by the cardiologists. One study patient had insufficient reperfusion (TIMI grade 2) after thrombus aspiration and balloon angioplasty; the remaining

Acute myocardial infarction (n=48)

PCI   (within 12 h)

Early contrast enhancement CT   (14±6 days)

Cardiopulmonary stress test (n=26) (3 months)

Echocardiography, BNP   (6 months)
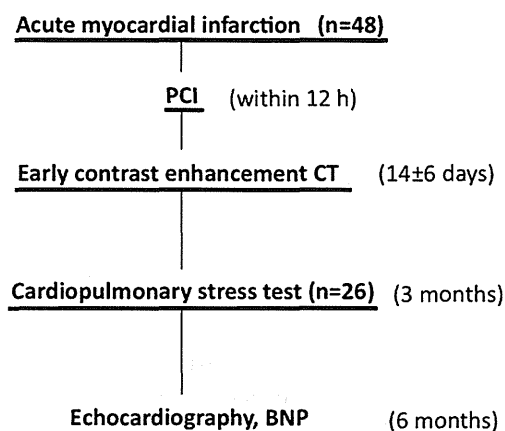
Fig. 1 Flow chart of study protocol. Patients with acute myocardial infarction who underwent percutaneous coronary intervention (PCI) and coronary computed tomography angiography (CTA) were enrolled in the study. All patients underwent coronary CTA within 14 ± 6 days after AMI onset. Of the 48 study patients, 26 underwent cardiopulmonary exercise test (CPX) 3 months after AMI onset

patients (TIMI grade 3) received stent implantation. TIMI grade [18] was assessed in each patient by coronary angiography after PCI. TIMI flow was categorized on a scale of 0–3 as follows: 0, absence of any antegrade flow beyond a coronary occlusion; 1, faint antegrade coronary flow beyond the occlusion with incomplete filling of the distal coronary bed; 2, delayed or sluggish antegrade flow with complete filling of the distal coronary bed; and 3, normal flow completely filling the distal coronary bed.

Acquisition and analysis of CT data

ECG-gated multidetector CTA was performed using a 64-slice CT scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) with a slice thickness of 0.5 mm, a tube voltage of 120 kV, a tube current of 350–500 mA, a relative pitch of 0.175–0.20, and a rotation time of 350–400 ms. Routine premedication with β-blockers was not employed, although β-blockers were administered when the resting heart rate was ≥75 beats/min. An 80-ml dose of nonionic iodinated contrast material containing 370 mg I/ml iopamidol (Iopamiron 370; Bayer, Osaka, Japan), followed by 40 ml of saline solution, was injected at a rate of 4 ml/s using a power injector (Dualshot; Nemoto, Tokyo, Japan). Nitroglycerin (0.3 mg) was sublingually administered for coronary artery dilatation. Scanning was performed during a single breath-hold lasting 10–20 s with automatic bolus tracking at 150 HU. Retrospective ECG gating with heart rate-adjusted gantry rotations of 350–400 ms was used for multisegmented reconstruction. The initial cardiac phase selected for reconstruction was centered at 75 % of the RR interval.

ImageXact® software (Toshiba Medical Systems) was used to select a single cardiac phase with minimal motion artifacts at mid-diastole or end-systole for reconstruction using a standard convolution kernel. We assessed the ED extent in longitudinal or 4-chamber views on multiplanar reconstruction images with a slice thickness of 3 mm, CT window width of 450–550, and a window level of 150–250 HU.

EDs on CTA were characterized by a low-attenuation area within the myocardium downstream of the culprit lesion. A standard algorithm was used to identify the coronary territory distribution and potential myocardial perfusion territories [19]. Figure 2 shows EDs and the myocardium downstream of the culprit lesions observed on CT images of an acute ST-segment elevation myocardial infarction after successful coronary stent implantation. A radiologist, who was blinded to the detailed patients' histories, visually assessed the mural extent. All patients were divided into the following 2 groups according to the extent of EDs: the EDs <75 % group (EDs <75 % of the left ventricular wall thickness, $n = 24$) or EDs $\geq$75 % group (EDs $\geq$75 % of the left ventricular wall thickness, $n = 24$). The extent was determined at the deepest site of EDs.

Cardiopulmonary exercise test

Of the 48 study patients, 26 underwent CPX 3 months after AMI onset. A MAT-2500 treadmill (Fukuda Denshi Co., Tokyo, Japan) was used to perform CPX. After an initial 3-min rest on the treadmill and a 3-min warm-up (speed 1.6 km/h; grade 0 %), patients underwent CPX at gradually increasing intensity (load increased at 1-min intervals). ECG was continuously monitored and blood pressure was measured at 1-min intervals. An expired gas analysis was performed throughout CPX using the breath-by-breath method and an AE-300S chart (Minato Medical Science, Osaka, Japan). VO_2, carbon dioxide production (VCO_2), and ventilation (VE) were measured; in addition, peak VO_2 was obtained. Moreover, the VE/VCO_2 slope was also calculated to assess exercise ventilatory efficiency. An apparent leveling off of lower limb muscle strength and orthopedic problems were taken as signs to terminate CPX.
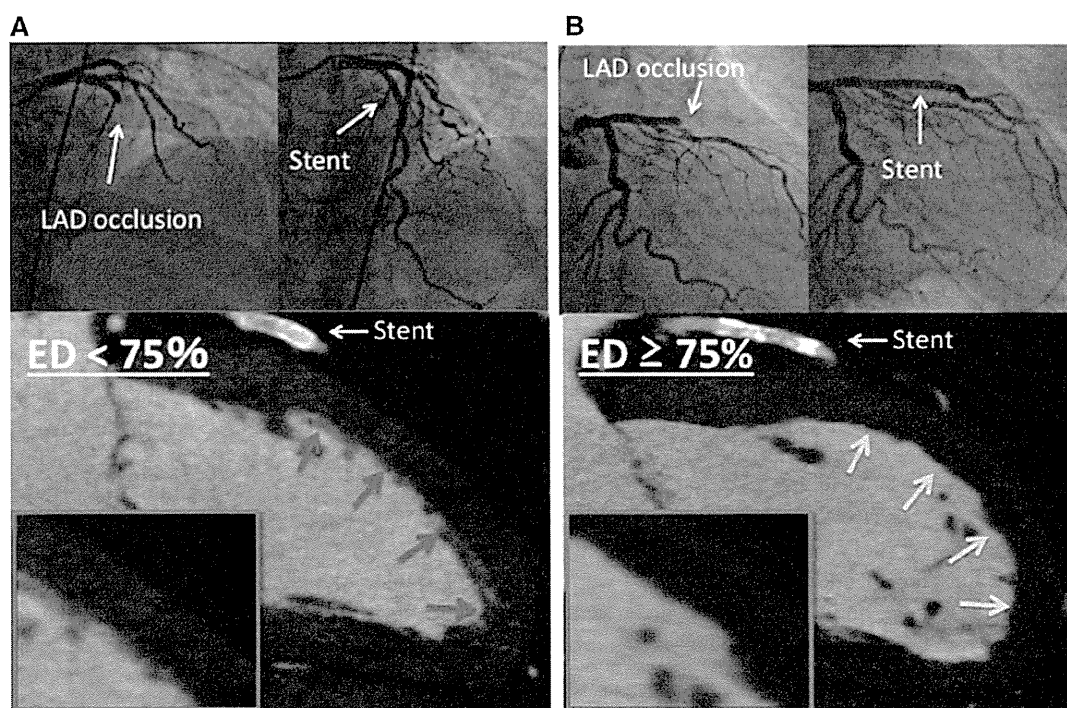
Fig. 2 Early defects (EDs) on computed tomography angiography (CTA) were characterized by a low-attenuation area within the myocardium downstream of the culprit lesion. Early defect and myocardium downstream of the culprit lesions shown on computed tomography angiography (CTA) in an acute ST-segment elevation myocardial infarction after successful coronary stenting. a Conventional coronary angiography shows total occlusion at the mid-left anterior descending artery (LAD), and a stent was successfully deployed at the culprit. Arrows show that early defects (EDs) <75 % on CTA visually depict subendothelial hypoattenuation in the territory of the LAD (also seen in the enlarged figure). b Conventional coronary angiography shows total occlusion at the mid LAD, and a stent was successfully deployed at the culprit. Long-axis early-pass perfusion CT image revealing EDs $\geq$75 % in the infarcted anterior area (see the arrows and the enlarged figure)

Blood sampling and echocardiography

Blood samples were collected before breakfast. BNP levels measured by fluorescent enzyme immunoassay were obtained 6 months after AMI onset. Comprehensive transthoracic echocardiography was also performed using commercially available ultrasound equipment (Aplio®; Toshiba, Tokyo, Japan) with a 3.5-MHz transducer 6 months after AMI onset. The biplane Simpson's method in the apical 4-chamber and 2-chamber view modes was used to measure LVEF [20].

Statistical analysis

Continuous variables are presented as the means ± standard deviations or medians with interquartile ranges (Q1–Q3), whereas discrete variables are presented as frequencies and percentages. The chi-squared test was used for the comparisons of categorical variables. The Mann–Whitney test was used to compare the 2 groups because of the relatively small sample size. The level of statistical significance was established at $P < 0.05$. The statistical analysis was performed using JMP10 software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The patients' baseline characteristics and medications administered 3 months after AMI onset are presented in Table 1. No significant differences were observed in gender, age, blood pressure and heart rate during CTA, or in the presence of coronary risk factors between the 2 groups. Moreover, no significant differences were observed in the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, or statins. Table 2 shows a summary of the areas damaged during AMI. Of the study patients, 15 had infarctions in the right coronary artery region, 28 had infarctions in the left anterior descending artery region, and 5 had infarctions in the left circumflex branch region. The success rate of PCI was 97.9 %. TIMI grade-3 flow in 1 patient was not obtained. Peak CK-MB levels were significantly higher in the EDs ≥75 % group than in the EDs <75 % group ($P < 0.001$).

Effects of myocardial EDs on CTA with exercise capacity, LVEF, and BNP levels in the chronic phase

Figure 3 shows the results of CPX recorded 3 months after AMI onset. There was no significant difference in peak

Table 1 Baseline characteristics

	EDs <75 % n = 24	EDs ≥75 % n = 24	P value
Age	59 ± 14	68 ± 8	0.156
Male/female	17/7	18/6	0.754
Hypertension, n (%)	14 (58.3)	19 (79.2)	0.12
Hyperlipidemia, n (%)	20 (83.3)	18 (75.0)	0.478
Diabetes, n (%)	6 (25.0)	7 (29.2)	0.745
Smoking, n (%)	14 (58.3)	14 (58.3)	0.859
Systolic blood pressure, mmHg	118 ± 18	120 ± 19	0.678
Diastolic blood pressure, mmHg	70 ± 12	70 ± 9	0.844
Heart rate, bpm	78 ± 16	75 ± 14	0.511
Medication, n (%)			
ACEI/ARB	23 (95.8)	23 (95.8)	1.000
β blocker	13 (54.2)	18 (75.0)	0.422
Calcium channel blocker	2 (8.3)	2 (8.3)	0.919
Statin	19 (79.2)	18 (75.0)	0.501

Data are shown as means ± standard deviations

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *EDs* early defects, *bpm* beats per minute

Table 2 Catheter findings and cardiac enzyme

	EDs <75 % n = 24	EDs ≥75 % n = 24	P value
Culprit vessel, n (%)			
RCA	6 (25.0)	9 (37.5)	0.06
LAD	13 (54.2)	15 (62.5)	
LCX	5 (20.8)	0 (0)	
PCI procedure, n (%)			
Stent	24 (100)	23 (95.8)	0.3122
POBA	0 (0)	1 (4.2)	0.3122
TIMI grade 3	24 (100)	23 (95.8)	0.3122
Infarcted size, ng/ml			
Peak CK-MB	210.8 (95.5–357.6)	409 (238.9–578)	<0.001

Data are shown as medians with Q1–Q3 interquartile ranges

LAD left anterior descending artery, *LCX* left circumflex artery, *PCI* percutaneous coronary intervention, *POBA* plain old balloon angioplasty, *RCA* right coronary artery, *TIMI* thrombosis in myocardial infarction

VO_2/kg between the 2 groups 3 months after AMI onset [ED <75 %: 29.8 ± 7.8 (median 28.3) ml/min/kg; ED ≥75 %: 25.7 ± 6.8 (median 24.7) ml/min/kg]. The VE/VCO_2 slope was significantly higher in the EDs ≥75 % group (28.7 ± 4.9; median 28.7) than in the EDs <75 % group [25.1 ± 3.1; median 24.8; ($P = 0.048$)]. Figure 4 shows LVEF and BNP levels obtained 6 months after AMI onset. LVEF in the chronic phase was significantly lower in the EDs ≥75 % group (48.1 ± 12.0 %; median 52.5) than
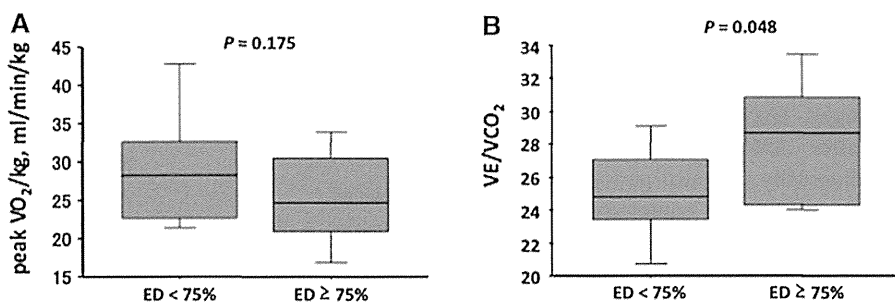
Fig. 3 Differences in exercise parameters for EDs assessed by CTA. *Box plots* have lines extending vertically from the boxes (*whiskers*) indicating variability outside the upper quartiles (Q3) and lower quartiles (Q1). Outliers are shown as *dots* if the individual data is either over the upper fence or lower fence. **a** There was no significant difference in peak VO_2/kg between the EDs <75 % group and the EDs ≥75 % group 3 months after AMI onset. **b** The VE/VCO_2 slope was significantly higher in the EDs ≥75 % group than in the EDs <75 % group

Fig. 4 Differences in cardiac parameters for EDs assessed by CTA. **a** Left ventricular ejection fraction at 6 months was significantly lower in the EDs ≥75 % group than in the EDs <75 % group. **b** Log of BNP levels 6 months after the AMI onset was significantly higher in the EDs ≥75 % group than in the EDs <75 % group
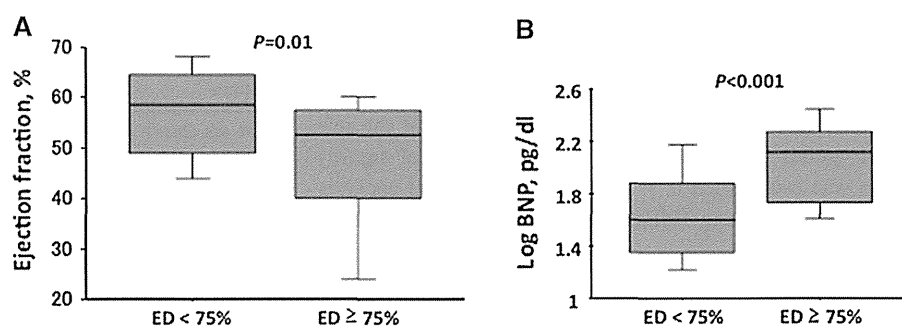
in the EDs <75 % group [56.8 ± 10.0 %; median 58.5 ($P = 0.01$)]. Visual wall thinning was more common in the EDs ≥75 % group (83 %) than in the EDs <75 % group [17 %, ($P < 0.001$)]. Log of BNP levels was higher in the EDs ≥75 % group (2.00 ± 0.35; median 2.09) than in the EDs <75 % group [1.61 ± 0.37; median 1.58 ($P < 0.001$)]. The maximum effective dose on CTA was 22.6 mSv.

Discussion

It is important to assess the mural extent of myocardial infarction, its location, wall motion recovery, and exercise capacity after AMI. In the present study, we demonstrated that ED extent within the infarcted myocardium on CTA after AMI influenced exercise capacity and cardiac function in the chronic phase.

After an intravenous bolus injection of contrast material, first-pass contrast-enhanced CT images, which vary with differences in attenuation, can be used to identify the areas of damaged myocardium. In the present study, EDs were seen in the myocardium downstream of the culprit lesions even though there was no significant epicardial coronary stenosis in the patients with AMI. In this regard, EDs on

CTA are possibly explained by abnormal blood flow in the myocardial capillaries; blood flow obstruction at the capillary level may be caused by tissue edema, necrosis, microembolism, or vasoconstriction [8, 12, 14]. Nieman et al. [11] found that EDs on CTA 5 days after AMI onset can clearly differentiate normal myocardium from infarcted myocardium: EDs on CTA were correlated with early perfusion defects shown by cardiac MRI. Koyama et al. [14] reported that 21 % of AMIs had no EDs on CTA but showed delayed enhancement; they stated that successful revascularization at both the epicardial coronary and microvascular levels could be achieved in their patients. Accordingly, EDs within the infarcted myocardium may not always represent the area of infarction; EDs might also represent abnormalities of the microvasculature after reperfusion in the case of patency in culprit lesions without distal embolisms of the epicardial coronary arteries. Consequently, although revascularization of epicardial coronary stenosis is necessary for myocardial salvage, successful revascularization of epicardial coronary stenosis is not equal to successful reperfusion of the microvasculature. Koyama et al. [14] also found that AMI patients with EDs had lower EF and greater peak cardiac enzyme levels than those without EDs. In the present study, the EDs ≥75 % group had higher peak CK-MB levels than the

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EDs <75 % group, which confirmed that ED extent may be closely associated with the infarcted myocardial volume. Thus, the assessment of EDs after reperfused AMI may indicate the severity of microvascular abnormalities and the location of the infarcted myocardium.

In the present study, EF in the chronic phase was significantly lower in the patients with larger EDs. Lessick et al. reported that the presence of EDs in CTA was closely related to myocardial dysfunction and poor recovery during the median 89-day follow-up in patients with AMI [8]. One study demonstrated that transmural infarction compared with subendocardial infarction assessed by EDs on CTA had poor wall motion recovery 6 months after anterior AMI [13]. The transmural extent of infarction detected by late gadolinium-enhanced (LGE) MRI predicted a progressive stepwise decrease in the likelihood of functional recovery despite successful coronary revascularization [21]. Segments presenting favorable recovery might have a significantly lower prevalence of EDs, which suggests that the presence and extent of EDs in CTA would probably predict recovery of cardiac function. In the present study, BNP levels in the chronic phase were greater in the patients with larger EDs. Omland et al. [22] reported that the determination of BNP levels provided important and independent prognostic information after AMI. These results might be attributed to decreased cardiac function remaining in the infarcted lesions. Larger EDs may indicate wider infarcted lesions, which suggests that LV systolic dysfunction may not be completely recovered, even in the chronic phase.

To date, no studies have reported the use of CTA as a predictor of exercise capacity after AMI onset. In the present study, exercise intolerance was common in the EDs ≥ 75 % group. Patients with chronic heart failure often have greater VE/VCO_2 slopes and VO_2 [23]. These parameters are recognized as useful predictors for prognosis. The VE/VCO_2 slope has been reported to be more accurate in the prognostic evaluation of cardiovascular prognosis [24, 25]. Accordingly, evaluation of the invasive extent of infarction on the basis of EDs on CTA probably predicts prognosis in patients with AMI. This study included a relatively small population and revealed no statistically significant associations between EDs and peak VO_2. Therefore, further data accumulation and studies are required for the assessment of this potential association. Finally, when the epicardial coronary arteries and the microvasculature were both considered, the presence of EDs on CTA after AMI was associated with worse functional outcomes, larger infarction, and exercise intolerance. Therefore, the evaluation of EDs on CTA in patients with ST-segment elevation AMI has therapeutic implications.

Study limitations

The present study had some limitations: (1) the number of patients was small, (2) the study was conducted retrospectively, (3) myocardial enhancement was not quantitatively measured, (4) the visual assessment of the extent of EDs on CTA was limited, and there was no assessment of the distribution of EDs, (5) because the study data were collected between 2005 and 2007, the radiation doses of coronary CTA were relatively high (recently developed dose-reduction techniques, such as dose modulation, iterative reconstruction, and step-and-shoot scans, were not available during the study period), (6) the scan timing for CT perfusion was suboptimal because dynamic CT was not used (moreover, myocardial perfusion can potentially change during the diastolic and systolic phases [26]), (7) LGE-MRI was not validated in this study, (8) CT was not performed in the chronic phase, and (9) the mechanism underlying the visualization of EDs on CTA was not elucidated. Further studies to address these issues are necessary.

Conclusion

Although there was no significant epicardial coronary stenosis, larger EDs on CTA in the acute phase of myocardial infarction influenced LV dysfunction and exercise intolerance in the chronic phase. CTA, an alternative method for evaluation of early perfusion in the infarcted myocardium, was useful for the prediction of future cardiac function.

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Presence of Neutrophil Extracellular Traps and Citrullinated Histone H3 in the Bloodstream of Critically Ill Patients

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Tomoya Hirose[1]*[∋][¶], **Shigeto Hamaguchi**[2∋][¶], **Naoya Matsumoto**[1], **Taro Irisawa**[1], **Masafumi Seki**[2], **Osamu Tasaki**[3], **Hideo Hosotsubo**[1], **Norihisa Yamamoto**[2], **Kouji Yamamoto**[4], **Yukihiro Akeda**[5], **Kazunori Oishi**[5], **Kazunori Tomono**[2], **Takeshi Shimazu**[1]

1 Department of Traumatology and Acute Critical Medicine, Osaka University Graduate School of Medicine, Osaka, Japan, 2 Division of Infection Control and Prevention, Osaka University Graduate School of Medicine, Osaka, Japan, 3 Department of Emergency Medicine, Unit of Clinical Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, 4 Department of Medical Innovation, Osaka University Hospital, Osaka, Japan, 5 International Research Center for Infectious Diseases, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

Abstract

Neutrophil extracellular traps (NETs), a newly identified immune mechanism, are induced by inflammatory stimuli. Modification by citrullination of histone H3 is thought to be involved in the in vitro formation of NETs. The purposes of this study were to evaluate whether NETs and citrullinated histone H3 (Cit-H3) are present in the bloodstream of critically ill patients and to identify correlations with clinical and biological parameters. Blood samples were collected from intubated patients at the time of ICU admission from April to June 2011. To identify NETs, DNA and histone H3 were visualized simultaneously by immunofluorescence in blood smears. Cit-H3 was detected using a specific antibody. We assessed relationships of the presence of NETs and Cit-H3 with the existence of bacteria in tracheal aspirate, SIRS, diagnosis, WBC count, and concentrations of IL-8, TNF-α, cf-DNA, lactate, and HMGB1. Forty-nine patients were included. The median of age was 66.0 (IQR: 52.5–76.0) years. The diagnoses included trauma (7, 14.3%), infection (14, 28.6%), resuscitation from cardiopulmonary arrest (8, 16.3%), acute poisoning (4, 8.1%), heart disease (4, 8.1%), brain stroke (8, 16.3%), heat stroke (2, 4.1%), and others (2, 4.1%). We identified NETs in 5 patients and Cit-H3 in 11 patients. NETs and/or Cit-H3 were observed more frequently in "the presence of bacteria in tracheal aspirate" group (11/22, 50.0%) than in "the absence of bacteria in tracheal aspirate" group (4/27, 14.8%) (p<.01). Multiple logistic regression analysis showed that only the presence of bacteria in tracheal aspirate was significantly associated with the presence of NETs and/or Cit-H3. The presence of bacteria in tracheal aspirate may be one important factor associated with NET formation. NETs may play a pivotal role in the biological defense against the dissemination of pathogens from the respiratory tract to the bloodstream in potentially infected patients.

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All data are included within the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: htomoya1979@hp-emerg.med.osaka-u.ac.jp

∋ These authors contributed equally to this work.

¶ These authors are joint first authors on this work.

Introduction

Neutrophils play an important role as the first line of innate immune defense [1]. One function of neutrophils, called "neutrophil extracellular traps" (NETs), has been discovered recently. NETs are fibrous structures that are released extracellularly from activated neutrophils in response to infection and also the sterile inflammatory process [2–5]. This distinctive phenomenon was first reported by Brinkmann et al in 2004 [6]. The main components of NETs are deoxyribonucleic acid (DNA) and histones H1, H2A, H2B, H3, and H4; other components such as neutrophil elastase, myeloperoxidase, bactericidal/permeability-

increasing protein, cathepsin G, lactoferrin, matrix metalloproteinase-9, peptidoglycan recognition proteins, pentraxin, and LL-37 have also been reported [5–11]. The type of active cell death involving the release of NETs is called NETosis [12], which differs from apoptosis and necrosis. Because formation of NETs does not require caspases and is not accompanied by DNA fragmentation, it is believed that this process is independent of apoptosis [12]. Despite several in vitro and animal experiments that have clearly shown the biological importance of NETs, little is known about the function of NETs in the human body [13,14].

Before the discovery of NETs, several studies reported on an increase in the concentration of circulating free DNA (cf-DNA) in