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【 ORIGINAL ARTICLE 】

Isometric Handgrip Stress Test during Right Heart Catheterization in Patients with Mitral Regurgitation -A Case Series Study-

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Abstract:

Objective The severity of mitral regurgitation (MR) dynamically changes during a stress test. Isometric handgrip is a readily-available stress test in daily practice; however, little is known regarding the response to isometric handgrip in MR patients during right heart catheterization. We aimed to evaluate this issue from our case-series study.

Methods We retrospectively investigated consecutive MR patients using the isometric handgrip stress test during right heart catheterization at our institution between October 2019 and April 2021. After resting measurements were obtained, sustained maximum-effort hand dynamometer grasping was maintained for about 2-3 minutes. We investigated the differences in right heart catheterization data between at rest and during handgrip, and evaluated the individual response to the isometric handgrip stress test.

Results We investigated a total of 15 patients (mean age: 75±6 years, moderate/severe MR: 7/8, primary/secondary MR: 8/7, mean left ventricular ejection fraction: 56±16%, exertional dyspnea: 10). During the handgrip test, the pulmonary capillary wedge pressure (PCWP) significantly increased [9 (8, 13) mmHg at rest to 20 (15, 27) mmHg during handgrip; $p<0.001$]. PCWP changes varied among individuals (range 2-22 mmHg) and were not correlated with patients' backgrounds including age, the natriuretic peptide levels, left ventricular ejection fraction, left atrial diameter or E/e' (all $p>0.05$). Patients with PCWP ≥25 mmHg during handgrip had a higher prevalence of exertional dyspnea than those without [6 (100%) vs. 4 (44%); $p=0.04$].

Conclusion We observed dynamic and varied hemodynamic changes during isometric handgrip in MR patients, suggesting that further research is needed to evaluate the clinical value of this maneuver.

Key words: isometric handgrip, mitral regurgitation, right heart catheterization

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Introduction

Mitral regurgitation (MR) is the most common valvular heart disease and it is a growing public health problem. The severity of MR dynamically changes during exercise or depending on the loading conditions, and its dynamic features have been suggested to explain the onset of exertional symptoms (1). Exercise stress tests are recommended for further evaluation among MR patients according to the situation (2, 3); however, they may not always be feasible and are unfortunately not widespread in daily practice.

Isometric handgrip is a simple and readily-available stress test (4). We previously reported a patient with moderate secondary MR and exertional dyspnea (5). In this case, isometric handgrip provoked a marked increase in the pulmonary capillary wedge pressure (PCWP), providing an important clue for elucidating the cause of dyspnea (5). Thus, we con-

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sidered isometric handgrip to play a potential role as a simple test based on this case and started to perform it on MR patients. To date, data about this test in MR patients are lacking, especially during right heart catheterization.

Accordingly, the aim of this case series study was to investigate the response to the isometric handgrip stress test during right heart catheterization in patients with MR.

Materials and Methods

Study design and population

We retrospectively investigated consecutive patients with MR using the isometric handgrip stress test during right heart catheterization at our institution between October 2019 and April 2021. There were no exclusion criteria. The decision to perform the handgrip stress test was at the discretion of the attending physicians. Each patient was placed in the supine position and underwent right heart catheterization through the femoral vein using a Swan-Ganz catheter. The right atrial pressure, right ventricular pressure, PCWP and main pulmonary artery pressure (PAP) were subsequently measured. The systemic arterial pressure was measured using an intra-arterial catheter indwelled for coronary angiography. After resting measurements were obtained, sustained maximum-effort handgrip grasping was maintained for at least one minute avoiding the Valsalva maneuver as much as possible. We used a hand dynamometer for the handgrip stress test during the study period. We continuously monitored the systemic artery blood pressure using an intra-arterial catheter during handgrip stress and when we confirmed the presence of sufficient stress, we promptly measured the systemic arterial blood pressure, heart rate, PCWP and PAP. PCWP and PAP were measured at end expiration. The duration of the isometric handgrip stress was determined on a case-by-case basis considering the changes in blood pressure and patient conditions, but it tended to be 2 to 3 minutes in almost all cases. This study was approved by the institutional review board of the National Hospital Organization Kyoto Medical Center (20-088) and conducted according to the Declaration of Helsinki.

Definition and measurements

We investigated detailed data of right heart catheterization at rest and during handgrip. We also collected the patient background data, laboratory data, symptom status, and echocardiographic data at the time of right heart catheterization. Echocardiographic examinations were performed using commercially available systems according to the guidelines (6). MR etiology was classified as either primary or secondary. The MR degree was graded qualitatively or semi-quantitatively based on the color jet area, flow convergence of regurgitation, cardiac chamber size, pulmonary vein flow, or velocity of trans-mitral E wave, according to the existing guidelines of valvular heart disease (3, 7).

Statistical analysis

Continuous variables are presented as the mean±standard deviation or median (interquartile range) according to the distribution. The group differences were compared using Fisher's exact test for dichotomous variables and the Mann-Whitney U test for continuous variables. The paired Wilcoxon test was applied to assess the difference in variables. The relationship between variables were determined by a Spearman correlation analysis. First, we evaluated the difference in right heart catheterization data between at rest and during handgrip. Second, we investigated the individual response to isometric handgrip during right heart catheterization. In addition, we evaluated the correlation between PCWP changes and the patients' characteristics. Third, as an exploratory analysis, we investigated the background differences between patients with PCWP ≥25 mmHg during handgrip and those without it by referring to previous reports (8, 9). All tests were two-tailed and a value of $p<0.05$ was considered to be significant. All analyses were performed using JMP version 14 (SAS Institute, Cary, USA).

Results

Baseline characteristics and hemodynamic changes during handgrip

During the study period, a total of 15 patients with MR underwent the isometric handgrip stress test during right heart catheterization. In 15 patients (mean age: 75±6 years, female: 8, moderate/severe MR: 7/8, primary/secondary MR: 8/7), the mean left ventricular ejection fraction was 56±16%, 10 had exertional dyspnea, and 3 had significant coronary artery stenosis (Table 1).

The hemodynamic pressure data at rest and during handgrip are shown in Table 2. The systemic blood pressure significantly increased during isometric handgrip ($p<0.001$), whereas the change of heart rate did not ($p=0.055$). The PCWP and mean PAP also significantly increased (both $p<0.001$). These results were also the case even after excluding patients with significant coronary disease.

Individual response to the handgrip stress test

The individual PCWP responses at rest and during handgrip are presented in Fig. 1. The median change in PCWP was 8 (6, 18) mmHg and varied among patients (minimum: 2 - maximum: 22 mmHg). There was no significant association between the PCWP change and patients' characteristics such as age (Spearman's $\rho=-0.12$, $p=0.68$), N-terminal pro B-type natriuretic peptide (NT-proBNP) level (Spearman's $\rho=0.19$, $p=0.49$), left ventricular ejection fraction (Spearman's $\rho=-0.36$, $p=0.18$), left atrial diameter (Spearman's $\rho=0.39$, $p=0.15$), baseline E/e' (Spearman's $\rho=-0.01$, $p=0.95$) or trans-mitral flow deceleration time (Spearman's $\rho=-0.21$, $p=0.45$) at baseline. Change in PCWP during handgrip and that in the systolic blood pressure were not significantly correlated

Table 1. Baseline Characteristics.

Patients	Age (years)	Sex	MR degree	MR etiology	LVDd (mm)	LVDs (mm)	LVEF (%)	LA diameter (mm)	E wave (cm/s)	DcT (s)	E/e'	NT-proBNP (ng/L)	Coronary artery disease	Exertional dyspnea
Case 1	80	Female	Moderate	Primary	41	27	64	40	103	189	12.7	669	None	Present
Case 2	61	Female	Severe	Primary	53	32	70	39	122	179	15.4	103	None	Absent
Case 3	80	Female	Severe	Primary	49	31	66	39	151	142	21.3	745	None	Present
Case 4	80	Female	Moderate	Secondary	56	46	48	52	82	171	9.1	1,047	RCA	Present
Case 5	70	Female	Moderate	Secondary	68	59	26	45	87	173	20.5	3,321	None	Present
Case 6	78	Male	Severe	Secondary	61	54	23	51	116	150	24.7	1,833	None	Present
Case 7	73	Female	Severe	Primary	42	24	74	41	162	179	14.6	2,474	None	Present
Case 8	82	Male	Severe	Secondary	46	29	61	51	119	142	18.9	20,132	None	Present
Case 9	73	Male	Moderate	Primary	53	34	65	43	97	105	11.7	6,553	None	Present
Case 10	83	Female	Moderate	Secondary	48	30	67	44	64	217	14.4	867	LAD	Absent
Case 11	74	Male	Severe	Secondary	73	47	64	77	146	178	15.4	474	None	Present
Case 12	78	Male	Moderate	Primary	51	33	64	44	57	200	6.5	69	None	Absent
Case 13	71	Male	Severe	Primary	47	33	57	42	96	192	9.9	36	None	Absent
Case 14	71	Male	Severe	Primary	47	31	63	37	72	201	10.3	89	LAD	Absent
Case 15	72	Female	Moderate	Secondary	55	48	32	33	82	204	17.0	1,400	None	Present

DcT: deceleration time, LA: left atrial, LAD: left anterior descending artery, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, LVEF: left ventricular ejection fraction, MR: mitral regurgitation, NT-proBNP: N-terminal pro B-type natriuretic peptide, RCA: right coronary artery.

Table 2. Changes of Hemodynamic Data during Isometric Handgrip Stress Test.

	At rest	During handgrip	p value
Systolic blood pressure (mmHg)*	145 (129, 163)	163 (149, 179)	<0.001
Diastolic blood pressure (mmHg)*	60 (55, 78)	77 (69, 81)	0.001
Heart rate (beats per minute)*	77 (66, 87)	79 (72, 87)	0.055
Systolic pulmonary artery pressure (mmHg)	29 (27, 39)	47 (38, 60)	<0.001
Diastolic pulmonary artery pressure (mmHg)	12 (8, 14)	20 (12, 26)	<0.001
Mean pulmonary artery pressure (mmHg)	19 (16, 22)	29 (24, 40)	<0.001
PCWP v wave (mmHg)	16 (13, 22)	35 (23, 39)	<0.001
PCWP mean (mmHg)	9 (8, 13)	20 (15, 27)	<0.001

*data during handgrip were available in 13 patients.
PCWP: pulmonary capillary wedge pressure

with each other (Spearman's ρ=-0.02, p=0.95).

Responses to the handgrip color-coded by the major characteristics are shown in Fig. 2. Patients with an elevated PCWP during handgrip (≥25 mmHg) accounted for 40% (6 patients) of the total. Patients with an elevated PCWP during handgrip had a higher prevalence of exertional dyspnea [6 (100%) vs. 4 (44%); p=0.04] than those without, whereas other clinical characteristics were comparable between the 2 groups.

Representative cases who concurrently underwent handgrip stress echocardiography

The data of handgrip stress echocardiography concurrently performed with right heart catheterization could be obtained in 2 cases during study period (*Case 4* and *Case 15*). In *Case 4*, as we previously reported, MR deteriorated from a moderate to severe grade during handgrip stress echocardiography. On the other hand, in *Case 15* (PCWP increased from 13 mmHg at rest to 27 mmHg during handgrip), degree of MR did not significantly change, whereas E/e' worsened from 17 at rest to 22 during handgrip stress echocardiography.

Discussion

In this case series study, we performed the isometric handgrip stress test during right heart catheterization in patients with MR. The isometric handgrip significantly increased the PCWP, and these changes varied among the patients.

Isometric handgrip test during catheterization in patients with MR

Previous studies suggested that the isometric handgrip stress increases the magnitude of MR as assessed by echocardiography (10, 11). However, the effects of isometric handgrip on invasive hemodynamical measurements in patients with MR have not been investigated. In this study, we revealed that the PCWP significantly increased by the isometric handgrip stress test in MR patients. Isometric hand-

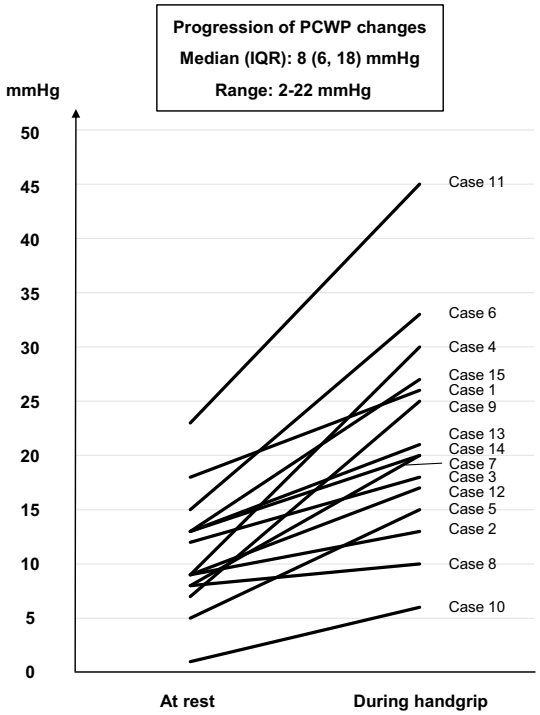

Figure 1. Individual response of PCWP to the isometric handgrip stress test in patients with mitral regurgitation. IQR: interquartile range, PCWP: pulmonary capillary wedge pressure

grip mainly causes an increase in blood pressure, with lesser effects on other parameters, including the heart rate (12, 13), as suggested in our study (18-mmHg increase in invasively measured systolic blood pressure, but only a 2-beats-per-minute increase in heart rate). Therefore, an increased afterload may play an important role in the dynamic PCWP changes in MR patients. However, the change in PCWP were neither significantly correlated with that in the systolic blood pressure nor with other baseline parameters, thus the exact mechanism of this response remains to be elucidated.

Importantly, an elevation of PCWP was theoretically caused by not only an MR increase but also left ventricular diastolic dysfunction (14), and impaired left atrial compliance (15). Distinguishing these mechanisms is impossible only with right heart catheterization and it requires echocardiographic evaluations. Our representative cases, as was shown in *Case 4* and *Case 15*, strongly suggested that echocardiography should be performed concurrently for elucidating the precise mechanism of PCWP elevation during handgrip. Further studies combined with right heart catheterization and echocardiography are required to investigate the hemodynamic changes induced by isometric handgrip in MR patients.

Clinical implications

Exercise stress tests are recommended in MR patients for the evaluation of their exertional symptoms (2). However, exercise tests using an ergometer usually require special equipment, and cannot be performed on elderly frail patients. On the other hand, the handgrip stress test is a simple and readily-available maneuver in almost all institutions. Our previous case report suggested the utility of isometric handgrip in elderly symptomatic MR patients (5). Recent study indicated that MR deterioration during handgrip was associated with New York Heart Association functional class (13). However, another recent study suggested the differential responses between handgrip stress and ergometer exercise in secondary MR patients, and raised a caution about handgrip stress test (12). First of all, we need to bear in mind that the ergometer and isometric handgrip are different types of exercise. Isometric handgrip is categorized as a static exercise in which blood pressure and afterload are mainly increased. Meanwhile, dynamic exercise, such as ergometer exercise, causes a relevant increase in the heart rate, cardiac output and oxygen consumption, and it is considered to be more physiological than the isometric handgrip (16). In addition, the stress load is not stable in isometric handgrip as compared with ergometer exercise. Therefore, further investigation is needed to address the clinical relevance of the handgrip stress test.

In this case-series, patients with PCWP ≥25 mmHg during handgrip had a higher prevalence of exertional dyspnea. Nevertheless, some patients complained of dyspnea even among those without an elevated PCWP during handgrip. Of note, the cut-off value used in this case series was based on the study using the supine ergometer among patients with heart failure, and it was not validated in patients with MR during handgrip test. Thus, this analysis should be cautiously interpreted. Recently, transcatheter therapy was approved for symptomatic MR patients and the evaluation of dynamic MR changes is therefore drawing increased attention. Some previous studies used the handgrip stress test to determine the indications for transcatheter mitral valve therapy (17-20). Intuitively, an increase in the regurgitation volume and/or elevation of PCWP during handgrip have worse prognostic impact on the patients with MR; however, some caution regarding the handgrip as mentioned above should be noted, and further data regarding the isometric handgrip in MR patients needs to be further collected to determine its diagnostic value and optimal threshold.

Study limitations

We acknowledged that this case series study is associated with several limitations. First, this was a single-center study with a relatively small sample size, subjecting it to biases inherent in such data. Due to the small number of the patients, we could not investigate the results divided by major characteristics and could not adjust the results by the confounders such as coronary artery disease. Second, exertional dyspnea was a subjective parameter and judged by the attending physicians merely based on a medical interview. Thus, objective measures such as the cardiopulmonary exercise test or 6-minute walk test are ideally needed, and further prospective follow-up regarding the endpoint such as heart failure events are warranted. Third, we performed iso-

Figure 2. **PCWP responses color-coded by the major characteristics. (A) Symptom status, (B) MR degree, (C) MR etiology. MR: mitral regurgitation, PCWP: pulmonary capillary wedge pressure**

metric handgrip only during right heart catheterization in most cases and were unable to address the precise mechanism of an increased PCWP. Fourth, we did not perform the exercise stress test concurrently, and we were unable to evaluate the differences in the hemodynamic changes between the isometric handgrip test and exercise test. Fifth, we did not determine the MR severity base on the quantitative parameters. Sixth, the maximum-effort handgrip method may not be a standard stress method (12, 21), and the duration of stress varied among the patients. Furthermore, we did not obtain any data regarding the maximum load. Seventh, we did not have any data regarding the response of handgrip stress in normal subjects. In addition, we did not obtain the data about cardiac output and systemic vascular resistance during the handgrip stress test. Thus, this report should be considered a hypothesis-generating case series, but we hope that this case series becomes the foundation for further research regarding the clinical value of the handgrip test in patients with MR in the future.

Conclusion

We reported our experience with the isometric handgrip stress test during right heart catheterization in patients with MR. We revealed dynamic PCWP changes during handgrip, and indicated that the individual responses might vary among the patients. Our case series suggested that further research is needed to evaluate the clinical utility of this maneuver in daily practice among patients with MR.

The authors state that they have no Conflict of Interest (COI).

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