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[Case Report]

Acute and chronic effects of mokuboito in a patient with heart failure due to severe aortic regurgitation

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Abstract

Medical treatment for heart failure is still limited in patients with symptomatic aortic regurgitation (AR). Here we report the effects of mokuboito used in combination with standard medical therapy for heart failure in an inoperable patient with symptomatic severe AR. We observed acute effects of mokuboito in decreasing systemic vascular resistance and increasing cardiac output, as well as its chronic effects in improving New York Heart Association class, plasma brain natriuretic peptide levels, and left ventricular diastolic function. Given its efficacy, the use of mokuboito might be an additional treatment for patients with heart failure.

Key words : Kampo medicine, mokuboito, heart failure, aortic regurgitation, systemic vascular resistance, cardiac afterload

Introduction

Patients with symptomatic heart failure due to aortic regurgitation (AR) have poor prognoses unless surgical treatment is performed. While aortic valve replacement is recommended for these patients, some cases are judged as inoperable due to complications, or the patient's poor general condition. Recently, trans-catheter aortic valve replacement has been reported in patients with AR, with limited applicability[1)]. In almost all inoperable cases, standard western medical procedures are performed to manage heart failure, which is particularly challenging for patients with AR.

Mokuboito is a traditional Kampo medicine in Japan and China, containing 1.5 g of dry extracts, which are extracted from 4 g of *Sinomeni Caulis et Rhizoma*, 3 g of *Cinnamomi cortex*, 3 g of *Radix ginseng*, and 10 g of *Gypsum fibrosum*. It is used for patients with heart failure accompanied by cyanosis, edema, cough, dyspnea, oliguria, or hardness of the epigastric region on physical examination[2)], and has been reported to be effective in treating heart failure[3-5)].

Honma *et al.* reported that mokuboito significantly improved the New York Heart Association (NYHA) functional classification and plasma brain natriuretic peptide (BNP) levels in patients with symptomatic heart failure (NYHA class II-III) in chronic phase[3)]. However, it has also been reported that mokuboito had no effect on cardiac parameters such as left ventricular ejection fraction (LVEF)[4,5)]. Moreover, it remains unclear whether mokuboito has acute effects on cardiac parameters in patients with heart failure.

We herein report the acute and chronic effects of mokuboito used in combination with standard western medical therapy for heart failure in an inoperable patient with symptomatic severe AR.

Case report

An 80-year-old man was admitted to our hospital for heart failure. He had a history of chronic

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kidney disease and was diagnosed with severe AR at age 71, for which he received no treatment.

One month before admission, he developed low output syndrome as well as multiple organ dysfunction syndrome following acute decompensated heart failure. As his condition improved with intensive care, including dobutamine and landiolol administration, mechanical ventilation, and continuous hemodiafiltration, surgical aortic valve replacement was considered. However, surgical intervention was deemed inappropriate given the high risk of mortality associated with advanced age and renal dysfunction (Japan score[6] : 17.8% for 30-day operative mortality ; 33.8% for 30-day operative mortality and major complications. Euro score : mortality 14.6%. STS score : mortality 5.1% ; morbidity and mortality 30.4%).

When the patient was referred to our hospital to continue treatment, he complained of exertional dyspnea and discomfort in the chest and epigastric region. On physical examination, he had an early diastolic murmur (Levine III/VI) over Erb's point, and a pansystolic murmur (Levine III/VI) over the apex, but no jugular venous distension or edema was observed. Chest X-ray on admission revealed mild cardiomegaly (cardiothoracic ratio, 56%) without any remarkable pulmonary congestion. An electrocardiogram showed chronic atrial fibrillation (AF) and left ventricular (LV) hypertrophy with strain pattern in V5 and V6 leads with premature ventricular contractions. Laboratory tests showed increased plasma BNP (1,406 pg/mL), chronic renal dysfunction, mild liver damage, and increased inflammatory reaction (Table 1). Echocardiography revealed a dilated left ventricle (LV end-diastolic dimension, 7.8 cm ; LV end-systolic dimension, 7.1 cm), LV systolic dysfunction (LVEF, 24.2%), severe AR (vena contracta width : 10 mm, central jet width : 78%, large jet density by continuous wave Doppler and enlarged LV), and moderate functional mitral regurgitation (MR) (effective regurgitant orifice area : 0.2 cm^2) (Fig. 1). The patient was diagnosed as having symptomatic severe AR (stage D).

The clinical course is shown in Fig. 2. Continuous administration of a β-blocker (bisoprolol patch [4 mg]) and diuretics (azosemide 30 mg, spironolactone 25 mg) did not improve the patient's symptoms (NYHA class III). Thus, bisoprolol was stopped on day 3, and low-dose carvedilol (1.25 mg) was started. On day 9, he could only walk 65 m during the 6-minute walk test (6MWT), giving up the test after 4 min due to dyspnea. To improve the symptoms, mokuboito was started as an additional therapy on day 11. Following this, his symptoms improved, and on day 22 he was able to walk 120 m in the 6MWT. His NYHA classification on day 33 was IIs, and his plasma BNP levels also decreased from 1406 to 627 pg/mL.

Table 2 shows echocardiography findings before and two months after mokuboito administration. While improvements were observed in symptoms and plasma BNP levels, LV dimension, LV systolic function (LVEF and S'), and MR grade remained unchanged during the follow-up period. There were, however, some improvements in estimated right ventricular pressure (eRVp) and LV diastolic function, i.e., decreased left atrial volume index by biplane Simpson's rule, peak E, E', and E/E'.

Since the patient was started on 1.25 mg carvedilol on day 3, which was increased to 10 mg

Table 1. Laboratory findings on admission.

White blood cell (/μL)	13000	AST (IU/L)	42
Neutrophil (%)	65.9	ALT (IU/L)	45
Lymphocyte (%)	21.0	ALP (IU/L)	349
Hemoglobin (g/dL)	12.6	γGTP (IU/L)	189
Platelet (10^3/μL)	24.4	Total bilirubin (mg/dL)	1.2
PT (s)	35	Creatine kinase (IU/L)	24
APTT (s)	51.7	Sodium (mEq/L)	135
FDP (μg/mL)	7.5	Potassium (mEq/L)	3.6
D-dimer (μg/mL)	0.4	Chloride (mEq/L)	95
C-reactive protein (mg/dL)	12.74	Urea nitrogen (mg/dL)	19.8
BNP (pg/mL)	1406	Creatinine (mg/dL)	1.34
Albumin (g/dL)	3.2	eGFR (mL/min/1.73 m^2)	40.0

PT : prothrombin time, APTT : activated partial thromboplastin time, FDP : fibrinogen and fibrin degradation product, BNP : brain natriuretic peptide, AST : aspartate aminotransferase, ALT : alanine aminotransferase, ALP : alkaline phosphatase, γGTP : γ-glutamyltranspeptidase, eGFR : estimated glomerular filtration rate

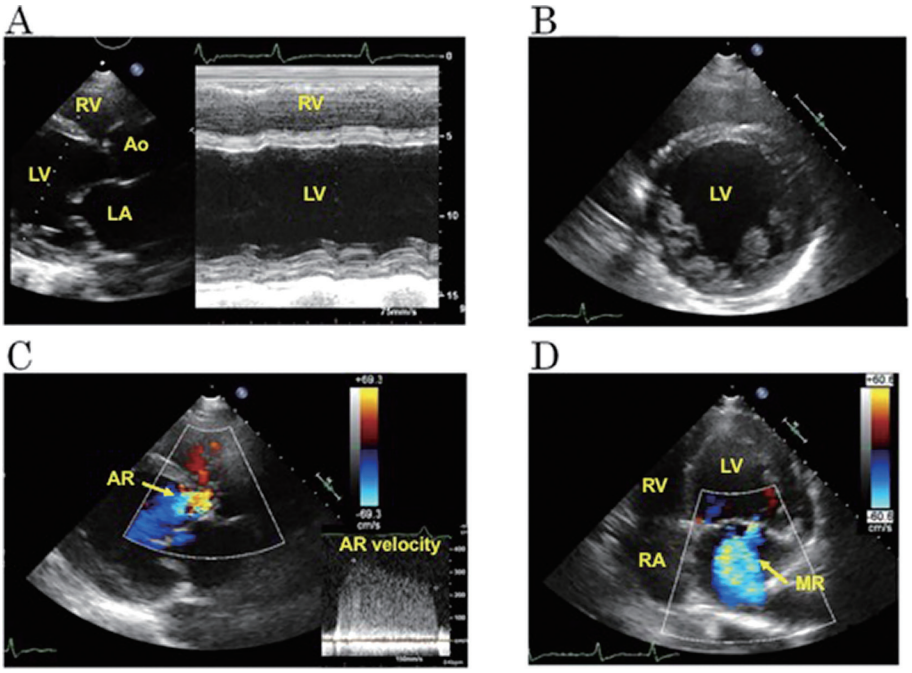

Fig. 1. Echocardiography on admission showed a dilated LV cavity (LV end-diastolic dimension, 7.8 cm ; LV end-systolic dimension, 7.1 cm) and reduced LV wall motion in the parasternal long-axis view (A) and short-axis view (B). Doppler echocardiography revealed severe aortic regurgitation (AR) (C) and moderate functional mitral regurgitation (MR) (D).
LV : left ventricle, RV : right ventricle, LA : left atrium, RA : right atrium, Ao : aorta.

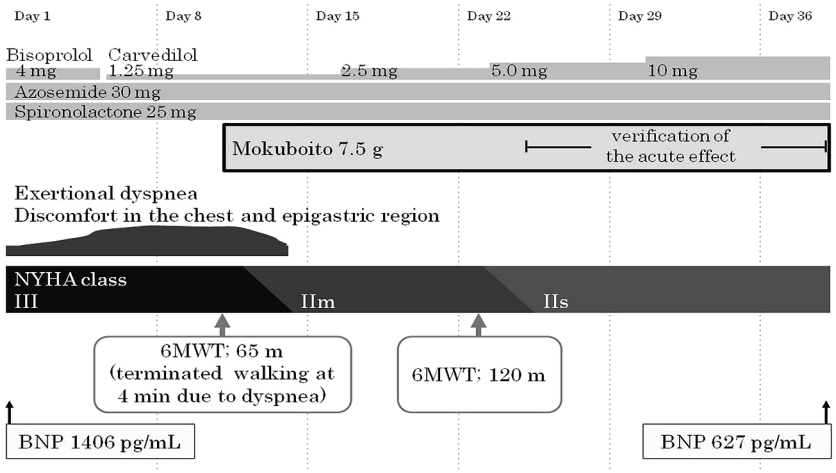

Fig. 2. The clinical course before and after administration of mokuboito with standard medical therapy. A β-blocker and diuretic drugs were administered continuously, but the patient's symptoms worsened (New York Heart Association [NYHA] functional classification III). After combination therapy with mokuboito, symptoms, NYHA class, and plasma BNP levels were improved. In the 6-minute walk test (6MWT), the patient was able to walk 120 m on day 22.

on day 30, whether the improvements in his symptoms were achieved through mokuboito or β-blocker therapy remains unclear. However, the patient felt his symptoms improving 15-20 min after mokuboito administration. Accordingly, we evaluated the acute effects of mokuboito on cardiac parameters from days 25 to 36.

Acute effects of mokuboito

After heart failure was controlled, we evaluated cardiac parameters repeatedly (13 times) before and 20 min after mokuboito administration to assess its acute effects from days 25 to 36.

The following parameters were assessed : sys-

Table 2. Changes in echocardiographic findings before and 2 months after mokuboito administration.

	Before administration	2 months after administration
LVDd [cm]	7.8	7.7
LVDs [cm]	7.1	6.6
EDV [mL]	236.0	220.0
ESV [mL]	179.0	167.0
LVEF [%]	24.2	24.1
LAVI [mL/m^2]	64.7	37.7
MR grade	Moderate	Moderate
ERO of MR [cm^2]	0.2	0.2
Peak E velocity [cm/s]	116.0	64.2
S' by TDI [cm/s]	5.1	5.0
E' by TDI [cm/s]	5.3	8.3
E/E'	21.8	7.8
eRVp [mmHg]	41.4	29.7

LVDd : left ventricular end-diastolic dimension, LVDs : left ventricular end-systolic dimension, EDV: end-diastolic volume, ESV: end-systolic volume, LVEF : left ventricular ejection fraction, LAVI : left atrial volume index, MR : mitral regurgitation, ERO : effective regurgitant orifice area, TDI : tissue Doppler imaging, eRVp : estimated right ventricular pressure

tolic blood pressure (sBP), diastolic blood pressure (dBP), mean blood pressure (mBP), heart rate (HR), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), +dP/dt, and eRVp. Doppler echocardiography was used to derive SV, +dP/dt, and eRVp. SV was calculated from LV outflow tract (LVOT) diameter and LVOT velocity time integral (VTI) : (LVOT diameter / 2)$^2 \times \pi \times$ LVOT VTI, and CO was calculated by SV $\times$ HR. At this time, LVOT diameter was adopted as the mean value of all measured values (2.63 cm), and LVOT VTI was measured as the average of five consecutive cardiac cycles because of irregular R-R intervals in AF rhythm[7,8]. SVR was estimated by the following formula : (mBP – central venous pressure [CVP]) / CO $\times$ 80, where CVP was fixed at 10 mmHg. To evaluate LV contractility, we estimated +dP/dt using a time interval (T) between 1 and 3 m/s on MR velocity determined by continuous wave Doppler ; dP/dt = 32 / T. We measured tricuspid regurgitation pressure gradient (TRPG) and approximated CVP by 10 mmHg. Estimated-RVp was calculated TRPG + 10 to evaluate pulmonary hypertension.

The values in Table 3 and Fig. 3 are expressed as mean ± SD. No significant differences in mean values as assessed by paired t-test were found in sBP, dBP, mBP, HR, +dP/dt, and eRVp before and after mokuboito administration. However, there were significant increases in SV and CO (SV : 107.3 ± 20.5 to 122.3 ± 15.3 mL, CO : 8.42 ± 1.46 to 9.48 ± 1.51 L/min, $P < 0.05$ for each) and a decrease in SVR (639.8 ± 117.8 to 548.3 ± 82.3 dynes·s/cm^5, $P < 0.05$).

Discussion

This is the first case report verifying the "acute effects" of mokuboito based on cardiac parameters in a patient with heart failure due to AR. Moreover, improvements were observed not only in symptoms and plasma BNP levels but also in LV diastolic function by "chronic effects" of mokuboito as an adjunct to a standard therapy including a β-blocker.

Mokuboito is a traditional Kampo medicine used in Japan and China to treat patients with heart

Table 3. Acute effects of mokuboito on cardiac parameters.

	Before	After	
sBP [mmHg]	107.8 ± 6.8	104.2 ± 8.8	n.s.
dBP [mmHg]	57.2 ± 3.8	56.8 ± 3.5	n.s.
mBP [mmHg]	74.0 ± 3.3	72.6 ± 3.6	n.s.
HR [bpm]	79.0 ± 8.5	77.4 ± 6.1	n.s.
SV [mL]	107.3 ± 20.5	122.3 ± 15.3	$P < 0.05$
CO [L/min]	8.42 ± 1.46	9.48 ± 1.51	$P < 0.05$
PVR [dynes·s/cm^5]	639.8 ± 117.8	548.3 ± 82.3	$P < 0.05$
+dP/dt [mmHg/s]	749.3 ± 118.2	757.5 ± 137.5	n.s.
eRVp [mmHg]	22.8 ± 4.7	21.9 ± 5.1	n.s.

sBP : systolic blood pressure, dBP : diastolic blood pressure, mBP : mean blood pressure, HR : heart rate, SV: stroke volume, CO : cardiac output, SVR : systemic vascular resistance, eRVp : estimated right ventricular pressure, n.s. : not significant
Before : before mokuboito administration, After : 20 min after mokuboito administration

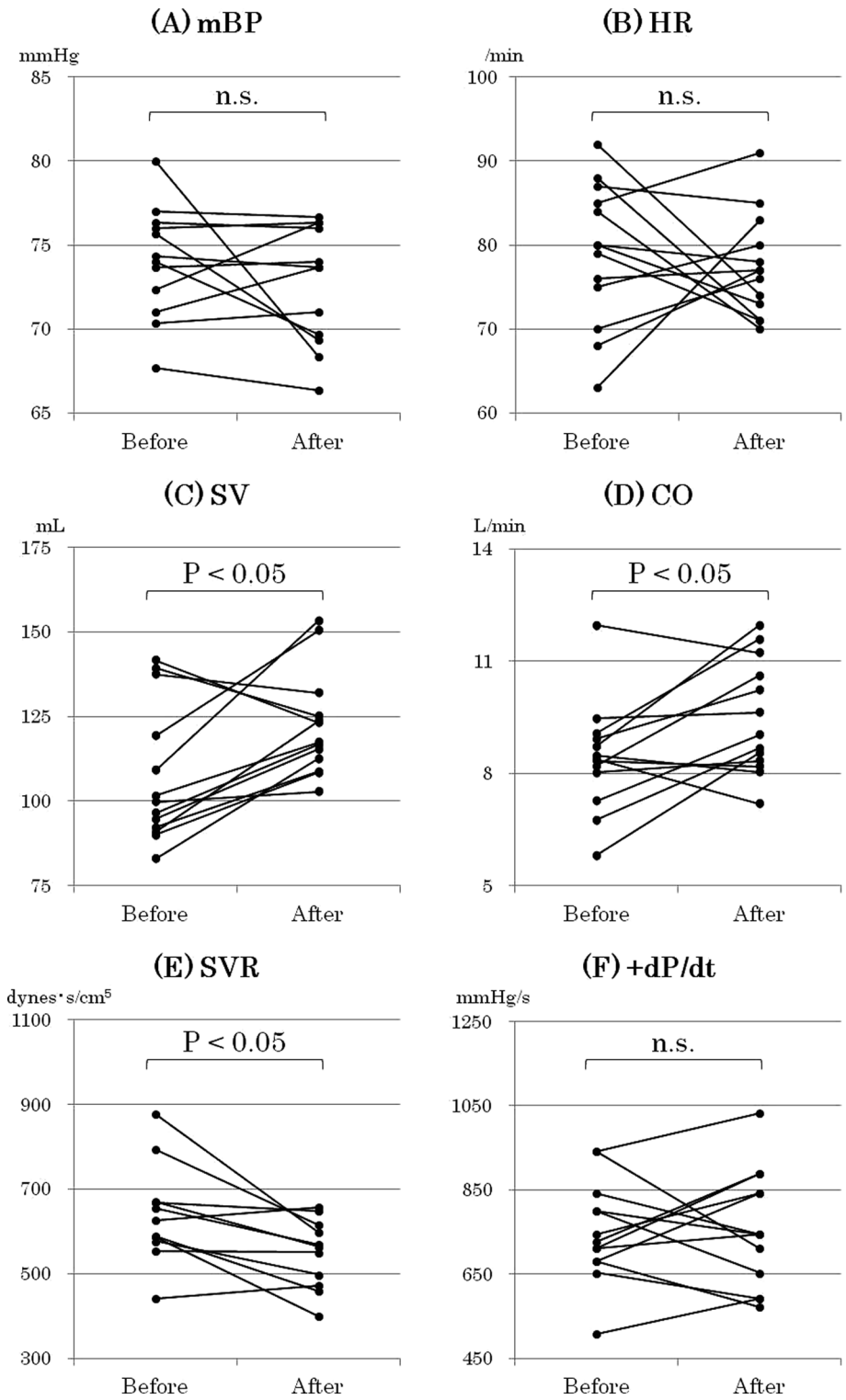

Fig. 3. The acute effects of mokuboito before and 20 min after administration were evaluated by mBP (A), HR (B), SV (C), CO (D), AVR (E), and +dP/dt (F). No differences were observed in mBP, HR, and +dP/dt before and after mokuboito administration, but there were significant increases in SV and CO, and a decrease in SVR, after mokuboito administration.
mBP : mean blood pressure, HR : heart rate, SV : stroke volume, CO : cardiac output, SVR : systemic vascular resistance.

failure as an additional therapy. A few clinical studies have evaluated the chronic effects of mokuboito in patients with heart failure[4,5], demonstrating its efficacy in improving NYHA classification and decreasing BNP levels, although no changes have been observed in LVEF, BP, HR, or cardiothoracic ratio. However, the chronic effects of mokuboito have not yet been adequately confirmed and, moreover, no objective evaluation has been performed with regard to its acute effects.

An animal study using rat aortas demonstrated the pharmacological actions of mokuboito (sinomenine, contained in *Sinomenium actum*)[9]. In that study, mokuboito and its constituents were shown to exert vasotonic-regulatory actions. Specifically, vasodilating actions were exerted on the constricted aorta via endothelium-dependent (i.e., prostacyclin and nitric oxide [NO] from the endothelium) and endothelium-independent (i.e., Ca^{2+} influx control on smooth muscle cells) mechanisms. On the other hand, vasoconstricting actions were exerted on the non-loaded aorta as mediated by α-adrenoreceptor stimulating action. It is possible that these vasotonic-regulatory actions contributed to the reduction in SVR observed in the present case.

In our patient, the observed acute effects suggest that mokuboito may reduce cardiac afterload by reducing SVR and increasing CO, even though cardiac contractility and BP remain constant. The vasodilating actions exerted by mokuboito may thus cause a reduction in SVR and an increase in CO, thereby leading to improvements in heart failure symptoms.

We also observed the chronic effects of mokuboito on LV diastolic function. However, it is unclear whether the acute effects of mokuboito (i.e., vasodilating actions) contribute to its chronic effects (i.e., improvements in symptoms and LV diastolic function) in patients with heart failure as an adjunct to a standard therapy including a β-blocker.

The effects of non-pharmacological therapies on cardiac function have been reported previously. For instance, sauna treatment reportedly improved vascular endothelial function, resulting in improved cardiac function as well as clinical symptoms[10]. Kihara *et al.* reported that SVR decreased after two weeks of sauna therapy, suggesting that that therapy improves endothelial function in resistance vessels. Improved endothelial function leads to vessel dilatation due to increased NO production. Moreover, decreased afterload after sauna therapy increased CO ; these changes led to improved peripheral circulation, which was responsible for improved clinical symptoms[10]. Given that sauna treatment also has an acute effect on vasodilation[11], this may lead to chronic improvement in patients with heart failure. In a similar manner, the acute vasodilation reaction caused by mokuboito may have chronic therapeutic effects.

Conclusion

We here reported the efficacy of mokuboito used in combination with standard medical therapy for heart failure in an inoperable patient with symptomatic severe AR. We observed the acute effects of mokuboito, decreasing SVR and increasing CO, as well as its chronic effects, which were improving NYHA class, plasma BNP levels, and LV diastolic function. Given its efficacy, we believe that the use of mokuboito is a possible additional treatment in patients with heart failure.

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