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SHORT COMMUNICATION

Does renin-angiotensin system inhibition have impacts on muscle mass and bone mineral density in heart failure patients?

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Abstract

Aims Results of experimental studies have indicated the possibility of muscle and bone mass being negatively regulated by renin-angiotensin system (RAS) activation, but that possibility has not been analysed in patients with heart failure (HF).

Methods and results Data for HF patients who received a dual-energy X-ray absorptiometry scan in our hospital were reviewed. Propensity scores for the use of RAS inhibitors (RASIs) were calculated using a multivariate logistic regression model to minimize selection bias. One hundred sixty pairs of patients were extracted. Plasma aldosterone concentration was significantly lower in the RASIs group than in the no-RASIs group (119 [IQR 71–185] vs. 94 [IQR 60–131] pg/mL, P = 0.003), confirming RAS inhibition in the RASIs group. Skeletal muscle mass index tended to be higher in the RASIs group than in the non-RASIs group (15.6 [IQR 14.0–17.2] vs. 15.0 [IQR 13.3–16.6] pg/mL, P = 0.065). The proportion of patients with muscle wasting, defined as appendicular skeletal muscle mass indexes of $<$7.00 and $<$5.40 kg/m^2 for males and females, respectively, was significantly lower in the RASIs group than in the non-RASIs group (53% vs. 64%, P = 0.041). Multivariate logistic regression analysis showed that the no use of RASIs was associated with presence of muscle wasting independently of age, presence of diabetes, renal function, and severity of HF. Bone mineral densities and proportions of patients with osteoporosis were similar in the two groups.

Conclusions Renin-angiotensin system inhibition is associated with a lower prevalence of muscle wasting in HF patients independently of established risk factors.

Keywords Heart failure; Renin-angiotensin system; Sarcopenia; Skeletal muscle; Osteoporosis; Propensity score matching

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Background

Renin-angiotensin system (RAS) inhibition by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers is an established approach to improve cardiac function and adverse outcomes including death in patients with heart failure (HF) with reduced ejection fraction. Importantly, the results of an observational study by Anker *et al*. revealed that weight loss of 6% or more during the follow-up period is the strongest predictor of impaired survival, and treatment with enalapril, an ACEI, reduced the risk of weight loss in HF patients who participated in the SOLVD and V-HeFT II trials, indicating the possible contribution of RAS activation to HF-induced wasting.[1] However, the effect of RAS inhibition on HF-induced alterations in body composition in humans has not been examined systematically.

Aims

The aim of this study was to determine the effects of RAS inhibition on muscle mass and bone mineral density (BMD) in HF patients.

Methods

This study was conducted in strict adherence with the principles of the Declaration of Helsinki and was approved by the Clinical Investigation Ethics Committee of Sapporo Medical University Hospital (Number 302-243).

This study was a single-centre, retrospective, and observational study. We enrolled consecutive patients who were admitted to our institute for diagnosis and management of HF during the period from 1 November 2015 to 31 May 2020. HF was diagnosed according to the Framingham criteria. Data for 499 patients were used for analyses after exclusion of patients with missing data.

Skeletal muscle mass (SSM) and appendicular skeletal muscle mass (ASM) were calculated by using a dual-energy X-ray absorptiometry scan (Horizon A DXA System, HOLOGIC, Waltham, MA, USA) as previously reported.[2,3] SSM index and ASM index (ASMI) were defined as SSM/height^2 and ASM/height,^{2} respectively. The cut-off values of ASMI for muscle wasting, that is, reduction in muscle mass, were $<$7.00 and $<$5.40 kg/m^2 for males and females, respectively, according to the criteria of the Asian Working Group for Sarcopenia and $<$6.87 and $<$5.46 kg/m^2 for males and females, respectively, according to the cut-off values for

Table 1 Baseline characteristics and medications

	Before propensity score matching				After propensity score matching			
	RASIs (−)	RASIs (+)			RASIs (−)	RASIs (+)		
	N = 254	*N* = 245	*P* value	SMD	*N* = 160	*N* = 160	*P* value	SMD
Baseline characteristics								
Age, *years*	74 [63, 82]	73 [62, 82]	0.493	0.032	74 [65, 82]	76 [65, 82]	0.704	0.021
Male, *n (%)*	120 (47%)	150 (61%)	0.002	0.275	85 (53%)	82 (51%)	0.737	0.038
NYHA functional class								
III, *n (%)*	27 (11%)	26 (11%)	0.066	0.210	16 (10%)	16 (10%)	0.993	0.014
III, *n (%)*	128 (50%)	147 (60%)			89 (56%)	88 (55%)		
III, *n (%)*	99 (39%)	72 (29%)			55 (34%)	56 (35%)		
Hypertension, *n (%)*	134 (53%)	186 (76%)	<0.001	0.498	106 (66%)	109 (68%)	0.721	0.040
Dyslipidaemia, *n (%)*	131 (52%)	132 (54%)	0.654	0.046	91 (57%)	89 (56%)	0.822	0.025
Diabetes mellitus, *n (%)*	87 (34%)	92 (38%)	0.456	0.069	65 (41%)	63 (39%)	0.820	0.026
Chronic kidney disease, *n (%)*	111 (44%)	94 (38%)	0.226	0.109	74 (46%)	72 (45%)	0.822	0.025
MNA-SF, *points*	9 [6, 11]	9 [7, 11]	0.295	0.115	9 [7, 11]	9 [7, 11]	0.834	0.002
Barthel index, *points*	80 [70, 90]	85 [70, 90]	0.206	0.102	85 [70, 90]	85 [70, 90]	0.996	0.008
Aetiology of heart failure								
Cardiomyopathy, *n (%)*	79 (31%)	89 (36%)	<0.001	0.489	62 (39%)	60 (38%)	0.864	0.096
Dilated cardiomyopathy	23 (9%)	51 (21%)			18 (11%)	38 (24%)		
Hypertrophic cardiomyopathy	16 (6%)	10 (4%)			13 (8%)	7 (4%)		
Others[a]	40 (16%)	28 (11%)			31 (19%)	15 (9%)		
VHD, *n (%)*	95 (37%)	76 (31%)			56 (35%)	62 (39%)		
IHD, *n (%)*	23 (9%)	55 (23%)			22 (14%)	18 (11%)		
Others[b], *n (%)*	57 (22%)	25 (10%)			20 (13%)	20 (13%)		
LVEF, %	55 [38, 64]	46 [32, 62]	<0.001	0.314	48 [34, 63]	52 [33, 64]	0.870	0.011
HFrEF, *n (%)*	69 (27%)	98 (40%)	0.003	0.308	54 (34%)	56 (35%)	0.284	0.041
HFmrEF, *n (%)*	40 (26%)	44 (18%)			29 (18%)	19 (12%)		
HFpEF, *n (%)*	143 (57%)	103 (42%)			77 (48%)	85 (53%)		
Medications								
Beta-blocker	148 (58%)	172 (70%)	<0.001	0.251	107 (65%)	105 (64%)	0.818	0.011
MRA	103 (41%)	111 (45%)	0.320	0.096	68 (41%)	76 (46%)	0.375	0.013
Loop diuretics	151 (59%)	127 (52%)	0.105	0.154	99 (60%)	97 (59%)	0.823	0.025
Statin	107 (42%)	124 (51%)	0.060	0.171	74 (45%)	75 (45%)	0.912	<0.001

HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MNA-SF, Mini Nutritional Assessment Short Form; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; RASIs, renin-angiotensin system inhibitors; SMD, standardized mean difference; VHD, valvular heart disease.

Data are presented as means ± standard deviation, median (interquartile range [IQR]), or percentage for variables. In the RASIs group, 55 patients received the treatment with ACEIs (enalapril, 46 patients, 3.2 ± 2.4 mg; imidapril, 9 patients, 5.8 ± 2.8 mg) and 105 patients received the treatment with angiotensin receptor blockers (losartan, 32 patients, 21.9 ± 18.2 mg; candesartan, 16 patients, 5.3 ± 2.6 mg; irbesartan, 5 patients, 90.0 ± 22.4 mg; telmisartan, 11 patients, 50.0 ± 30.0 mg; olmesartan, 17 patients, 16.2 ± 8.2 mg; azilsartan, 11 patients, 23.6 ± 11.2 mg; valsartan, 13 patients, 66.2 ± 22.2 mg).

[a]Others include arrhythmogenic cardiomyopathy, secondary cardiomyopathies, and unclassified cardiomyopathy.

[b]Others are shown in the Supporting Information, *Table S1*.

Table 2 Anthropometric parameters and laboratory data

	Before propensity score matching				After propensity score matching			
	RASIs (−)	RASIs (+)			RASIs (−)	RASIs (+)		
	N = 254	*N* = 245	*P* value	SMD	*N* = 160	*N* = 160	*P* value	SMD
Anthropometric parameters								
Height, *cm*	157 [150, 165]	160 [153, 167]	0.005	0.235	158 [150, 166]	158 [151, 166]	0.715	0.039
Body weight, *kg*	52.6 [46.0, 62.5]	58.4 [50.1, 69.6]	<0.001	0.366	54.8 [47.3, 65.2]	55.8 [47.2, 67.0]	0.475	0.041
BMI, kg/m^2	21.6 [19.6, 24.1]	23.2 [20.4, 25.4]	<0.001	0.307	22.0 [19.8, 24.1]	22.6 [20.1, 24.6]	0.141	0.063
FMI, kg/m^2	6.24 [4.53, 7.94]	6.47 [5.16, 8.53]	0.040	0.148	6.42 [4.89, 8.08]	6.42 [5.28, 8.00]	0.781	0.025
Laboratory data								
NT-proBNP, *pg/mL*	1111 [437, 2718]	1114 [431, 2552]	0.997	0.108	1148 [636, 2718]	1109 [441, 2840]	0.580	0.024
Albumin, *mg/dL*	3.6 [3.3, 3.9]	3.6 [3.3, 4.0]	0.793	0.070	3.6 [3.3, 4.0]	3.6 [3.3, 3.9]	0.966	0.062
Cystatin C, *mg/dL*	1.17 [0.95, 1.62]	1.17 [0.97, 1.61]	0.868	0.054	1.19 [0.99, 1.61]	1.23 [1.00, 1.67]	0.549	0.009
eGFRcys, $mL/min/1.73\ m^2$	55.6 [38.3, 69.5]	57.4 [38.0, 71.5]	0.616	0.042	56.3 [39.0, 67.2]	52.6 [35.2, 70.3]	0.657	0.012
Fasting glucose, *mg/dL*	88 [80, 99]	91 [82, 106]	0.063	0.104	90 [81, 104]	90 [82, 103]	0.952	0.081
HbA1c, %	5.8 [5.5, 6.3]	6.0 [5.6, 6.3]	0.062	0.094	5.9 [5.5, 6.4]	6.0 [5.6, 6.4]	0.588	0.019
Triglyceride, *mg/dL*	95 [71, 127]	103 [77, 132]	0.153	0.068	96 [69, 130]	99 [77, 128]	0.959	0.096
HDL-cholesterol, *mg/dL*	52 [42, 62]	48 [38, 59]	0.016	0.156	50 [40, 61]	49 [39, 62]	0.636	0.012
LDL-cholesterol, *mg/dL*	95 [76, 119]	92 [73, 113]	0.220	0.089	92 [74, 115]	89 [71, 116]	0.723	0.017
PRA, *ng/mL/h*	1.5 [0.5, 5.4]	2.1 [0.6, 7.1]	0.211	0.006	1.5 [0.5–5.0]	1.9 [0.6–7.1]	0.165	0.017
Aldosterone, *pg/mL*	116 [71, 189]	96 [63, 139]	<0.001	0.363	119 [71, 185]	94 [60, 131]	0.003	0.348
Cortisol, *μg/dL*	11.6 [8.2, 14.4]	11.8 [8.7, 14.7]	0.440	0.027	11.2 [8.0, 13.8]	11.8 [8.5, 14.7]	0.412	0.018
ACTH, *pg/mL*	33.9 [19.4, 50.8]	34.1 [17.2, 50.3]	0.881	0.026	34.2 [19.7, 51.6]	32.6 [15.7, 48.8]	0.535	0.099
Cortisol/ACTH	0.32 [0.22, 0.47]	0.34 [0.22, 0.58]	0.262	0.004	0.30 [0.21, 0.45]	0.35 [0.22, 0.62]	0.102	0.016

ACTH, adrenocorticotropic hormone; BMI, body mass index; eGFRcys, estimated glomerular filtration rate calculated by the cystatin C-based equation; FMI, fat mass index; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRA, plasma renin activity; RASIs, renin-angiotensin system inhibitors; SMD, standardized mean difference.

Data are presented as means ± standard deviation, median (interquartile range [IQR]), or percentage for variables. In the RASIs group, 55 patients received the treatment with ACEIs and 105 patients received the treatment with angiotensin receptor blockers. SMD is used as a balance measure of individual covariates before and after propensity score matching.

Japanese developed by Sanada *et al*. that are values two standard deviations below the sex-specific means of young adults aged 18–40 years.[4] BMDs at the hip with the femoral neck and at the lumbar spine over the L2–L4 regions were measured and expressed as g/cm^2. Diagnosis of osteoporosis was made when BMD at either of the two sites was less than 70% of Young Adult Mean.

Data are presented as medians (interquartile range [IQR]: 25th to 75th percentile) and expressed as frequency and percentage. The sample size to detect 10% difference in proportion of muscle wasting between the two groups was determined by using the formula with α = 0.05, statistical power = 0.80, effect size = 0.20, and the required sample size was 190 patients. In post hoc analyses, the statistical power in the present study was 98% (AGWS) and 99% (Sanada *et al*.), respectively. Inter-group differences for continuous variables and categorical variables were tested using the unpaired Student's *t*-test or Welch's *t*-test. To minimize selection bias in a retrospective study, propensity score matching (1:1 match, nearest neighbour matching, C-statistics = 0.73) was performed according to potential covariates (age, sex, height, fat mass index, hypertension, dyslipidaemia, diabetes mellitus, chronic kidney disease, HF aetiology, New York Heart Association functional class, left ventricular ejection fraction, nutritional status according to the Mini Nutritional Assessment Short Form, and use of beta blockers, mineralocorticoid receptor antagonists, loop diuretics, and statins) and a standardized mean difference of more than 0.1 was defined as a meaningful difference. The statistical significance level was set to $P < 0.05$. Statistical analyses were performed using JMP Version 14.3.0 (SAS Institute Inc., Cary, NC, USA) and R Version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics of heart failure patients before and after propensity score matching

Patients receiving renin-angiotensin system inhibitors (RASIs) were more frequently male, younger, taller, and heavier than patients in the no-RASIs group, resulting in higher fat mass index and lower HDL-cholesterol in patients receiving RASIs. Patients in the RASIs group had significantly higher rates of ischaemic heart disease and hypertension than did patients in the no-RASIs group. After propensity score matching, differences in incorporated covariates were substantially improved (*Tables 1* and *2*). Plasma aldosterone concentration was

Figure 1 (A, B) Appendicular skeletal muscle mass index (ASMI, A) and skeletal muscle mass index (SSMI, B) in patients receiving renin-angiotensin system inhibitors (RASIs) and patients not receiving RASIs. (C) Proportions of patients with muscle wasting in patients receiving RASIs and patients not receiving RASIs. The cut-off values of ASMI for muscle wasting, that is, reduction in muscle mass, were <7.00 and <5.40 kg/m^2 for males and females, respectively, according to the criteria of the Asian Working Group for Sarcopenia (AWGS) and <6.87 and <5.46 kg/m^2 for males and females, respectively, according to the criteria for Japanese developed by Sanada *et al*.[4] (D) Because there are differences in ASMI between males and females, heart failure patients were subdivided into tertiles within sex as follows: first tertile, <6.04 kg/m^2 in males and <4.81 kg/m^2 in females; second tertile, 6.04 to <7.04 kg/m^2 in males and 4.81 to <5.64 kg/m^2 in females; third tertile, ≥7.04 kg/m^2 in males and ≥5.64 kg/m^2 in females.

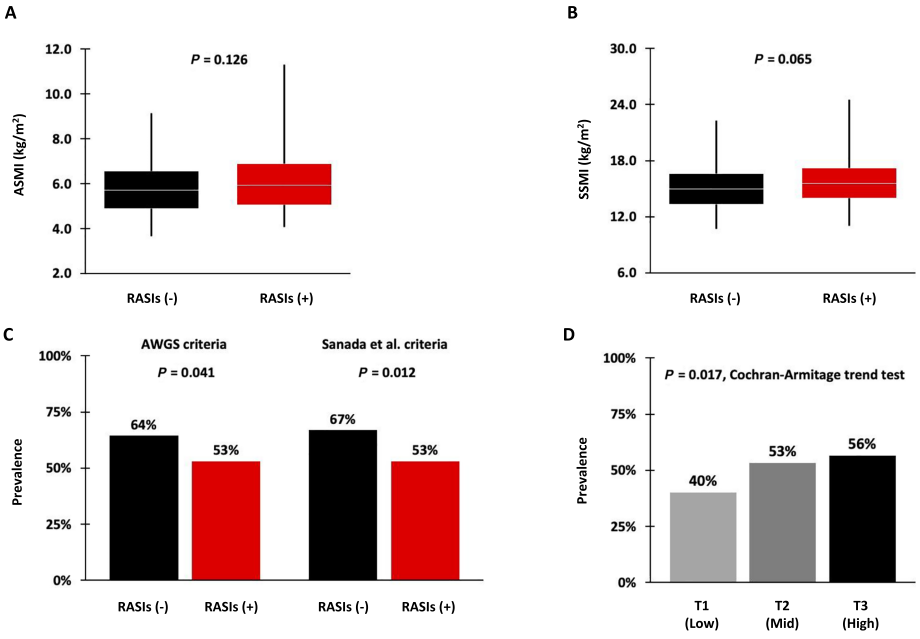

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Table 3 Impacts of renin-angiotensin system inhibitors use on muscle wasting

	AWGS criteria		Sanada *et al*. criteria	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Univariate model	0.63 (0.40, 0.98)	0.041	0.56 (0.36, 0.88)	0.012
Multivariate				
Model 1	0.63 (0.40, 0.99)	0.043	0.56 (0.35, 0.88)	0.012
Model 2	0.58 (0.35, 0.96)	0.034	0.52 (0.31, 0.85)	0.010

ASMI, appendicular skeletal muscle mass index; AWGS, Asian Working Group for Sarcopenia; eGFRcys, estimated glomerular filtration rate calculated using cystatin C; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Adjusted multivariate models: Model 1, age + sex; Model 2, Model 1 + LVEF, diabetes mellitus, eGFRcys, and log NT-proBNP. The cut-off values of ASMI for muscle wasting, that is, reduction in muscle mass, were <7.00 and <5.40 kg/m^2 for males and females, respectively, according to the criteria of the AWGS and <6.87 and <5.46 kg/m^2 for males and females, respectively, according to the criteria for Japanese developed by Sanada *et al*.[4] $P < 0.05$ was considered statistically significant.

significantly lower in the RASIs group than in the no-RASIs group, indicating that the effect of RAS inhibition in the RASIs group was preserved after propensity score matching.

Association of renin-angiotensin system inhibitors use with muscle wasting in heart failure patients

Skeletal muscle mass index, but not ASMI, tended to be higher in the RASIs group than in the no-RASIs group (15.7 [IQR 14.0–17.2] vs. 14.9 [IQR 13.6–16.6] kg/m^2, $P = 0.065$, *Figure 1A,B*). The proportion of patients with muscle wasting was lower in the RASIs group than in the no-RASIs group (*Figure 1C*). Patients were subdivided into tertiles within sex according to ASMI levels and then combined to avoid sex differences. The proportion of patients receiving RASIs was lower in HF patients with a low tertile of ASMI, whereas it was higher in HF patients with a high tertile of ASMI (*Figure 1D*). In multivariate logistic regression analysis, use of RASIs was selected as an independent explanatory factor

Figure 2 (A, B) Bone mineral densities (BMDs) at the femoral neck (A) and lumbar spine (B) in patients receiving renin-angiotensin system inhibitors (RASIs) and patients not receiving RASIs. (C) Proportions of patients with osteoporosis in patients receiving RASIs and patients not receiving RASIs. Diagnosis of osteoporosis was made when BMD at either of the two sites was less than 70% of Young Adult Mean. (D) Because there are differences in BMD at lumber spine between males and females, heart failure patients were subdivided into tertiles within sex as follows: first tertile, <0.947 g/cm^2 in males and <0.773 g/cm^2 in females; second tertile, 0.947 to <1.165 g/cm^2 in males and 0.773 to <0.932 g/cm^2 in females; third tertile, ≥1.165 g/cm^2 in males and ≥0.932 g/cm^2 in females.

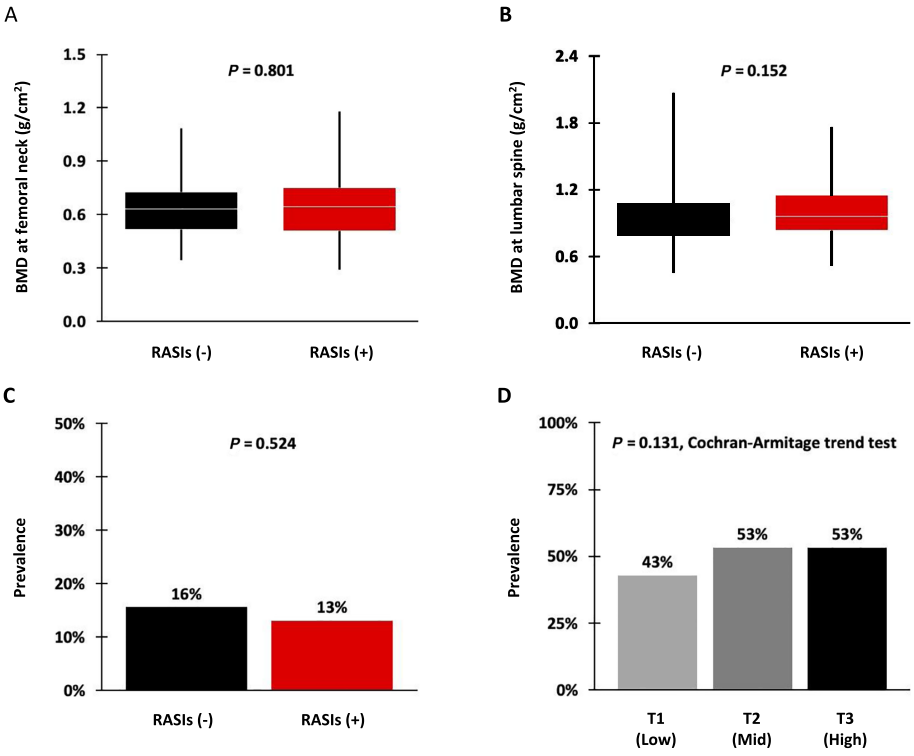
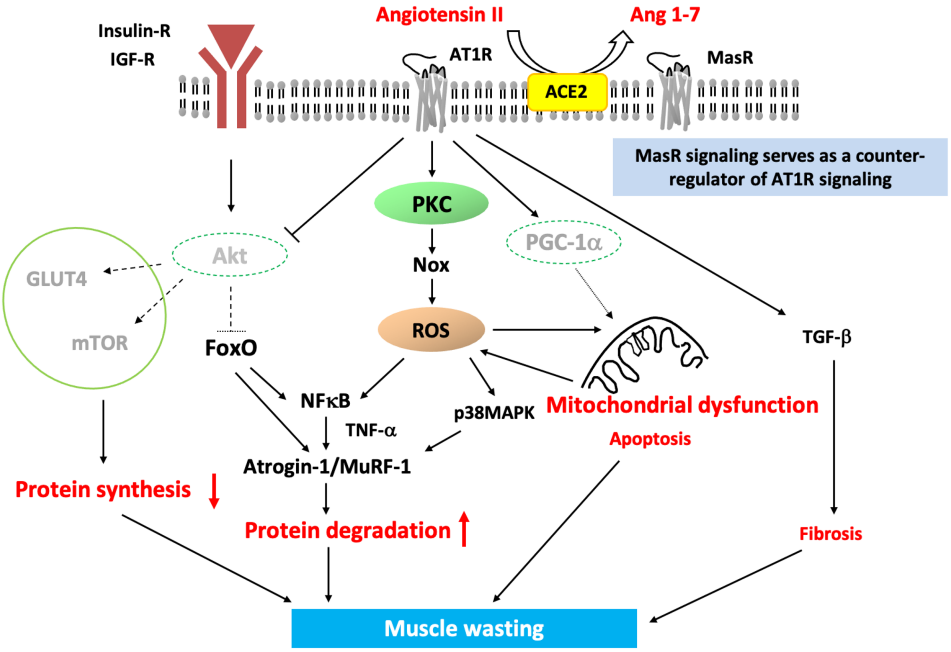


Figure 3 The mechanism by which angiotensin receptor signalling induces muscle wasting. ACE2, angiotensin-converting enzyme 2; Ang 1–7, angiotensin 1–7; AT1R, angiotensin type 1 receptor; FoxO, forkhead box O; GLUT4, glucose transporter type 4; MasR, Mas receptor; mTOR, mammalian target of rapamycin; MuRF, muscle-specific RING finger; NF-κB, nuclear factor-kappa B; Nox, NADPH oxidase; PGC-1, peroxisome proliferator-activated receptor γ coactivator-1; R, receptor; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumour necrosis factor.



of the presence of muscle wasting after adjustment for known modulators of muscle mass, that is, age, left ventricular ejection fraction, diabetes mellitus, estimated glomerular filtration rate calculated using cystatin C, and N-terminal pro-B-type natriuretic peptide (*Table 3*).

As shown in *Figure 2*, BMDs at the femoral neck and lumbar spine and the proportions of patients with osteoporosis were similar in the two groups, although the proportion of patients receiving RASIs tended to be lower in HF patients with a low tertile of BMDs.

Conclusions

Muscle wasting is frequently observed in HF patients and has been shown to be associated with lower exercise capacity and poor prognosis.[5,6] HF-induced muscle wasting is primarily attributable to immobility caused by lower exercise capacity and malnutrition induced by anorexia or malabsorption due to intestinal congestion. Protein catabolism is promoted by HF-induced stimulation of the inflammatory cascade and neurohormonal systems, one of which is RAS.[3,6] Although results of experimental studies using HF models showed that treatment with RASIs improved muscle dysfunction and atrophy, improvement of haemodynamics such as afterload reduction and anti-remodelling effects is unlikely to be a sole mechanism of favourable effect of RAS inhibition on muscle wasting because protective actions of RASIs on muscle wasting were found also in non-HF models.[6–8] The stimulation of angiotensin type 1 receptor, which is highly expressed in skeletal muscle cells, suppresses Akt activity, leading to reduction in mTOR complex 1-mediated protein synthesis, whereas it promotes activation of the ubiquitin proteasome system through elevation in atrogin-1/muscle-specific RING finger 1 expression by multiple mechanisms, leading to protein degradation (*Figure 3*).[6–9] These untoward effects of angiotensin type 1 receptor activation on skeletal muscle cells are mitigated by the treatment with RASIs. In addition, the protective action of RASIs on muscle dysfunction and atrophy may be mediated by angiotensin-converting enzyme 2-mediated angiotensin (1–7) generation according to results of very recent experimental studies.[10] There have been several studies showing the effects of RASIs on muscle mass in a cohort of community-dwelling elderly people.[11–13] An earlier study showed that the mean 6 min walking distance was significantly improved in functionally impaired elderly people who received administration of an ACEI, although a conflicting finding was also reported.[11,12] Results of a study by Spira *et al*. showed that users of ACEIs had had lower lean mass relative to fat mass, leading to the conclusion that ACEI users have lower muscle mass relative to fat mass.[13] On the other hand, the use of RASIs was associated with a lower prevalence of muscle wasting after adjustment for multiple covariates including fat mass in the present study. These findings suggest that the contribution of RAS activity to muscle

wasting is large in HF patients although its contribution differs depending on the background morbidity in patients.

Results of experimental studies revealed that circulating angiotensin II and local RAS negatively regulate BMD through various mechanisms including production of receptor activator of nuclear factor-kB ligand.[14] However, clinical studies in which the effect of RASIs on BMD was analysed yielded inconsistent findings.[14] These conflicting reports cannot be easily reconciled; however, differences in study protocols (observational or prospective), menopausal status, and types of concomitant medications might be responsible. Further analyses are needed to demonstrate the effect of RAS inhibition on BMD in HF patients.

There are limitations in the present study. First, this study was a retrospective observational study using a small number of Japanese patients. Second, patients with various aetiologies of HF including secondary cardiomyopathies were included in the analyses of the present study. Third, we enrolled consecutive patients who were admitted to our institute for diagnosis and management of HF. Patients who were hospitalized for the first time for HF and patients who were diagnosed as having co-morbidities such as hypertension, diabetes mellitus, and chronic kidney disease after the admission were included in the analyses of the present study, leading to selection bias in study subjects. Considering the heterogeneity of the study subjects, the propensity score-matched analyses were performed in the present study. Fourth, although renal function was successfully balanced after the propensity score matching (an standardized mean difference, 0.012), a slight difference between the RASIs group and the no-RASIs group still remains. Fifth, information on physical activity was not available in the present study, although the basic activity of daily living assessed by the Barthel index was similar in the two groups after the propensity score matching. Finally, an obvious limitation in the present study is the lack of information on RASIs treatment periods.

Conflict of interest

None declared.

Funding

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Etiology of heart failure.

References

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