

Cardiac function response to stenting in atherosclerotic renal artery disease with and without heart failure: results from the Carmel study

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Abstract

Aims Consensus-derived guidelines recommend renal stenting for patients with atherosclerotic renal artery disease (ARAD) and heart failure (HF). The aim of this prospective multi-centre observational study was to verify our hypothesis that changes in E/e' , an echocardiographic correlate of left ventricular (LV) filling pressure, following renal stenting may differ between ARAD patients with and without HF.

Methods and results This study enrolled *de novo* ARAD patients undergoing renal stenting at 14 institutions. The primary endpoint was the difference in E/e' change between ARAD patients with and without HF. Clinical and echocardiographic data were prospectively collected at baseline, the day following renal stenting, and 1 month and 6 months afterwards. ARAD patients with HF were defined as patients with New York Heart Association (NYHA) Class 2 and more, or a history of HF hospitalization. A total of 76 patients were included, and 39% were ARAD patients with HF. ARAD patients with HF had significantly lower estimated glomerular filtration rate ($P = 0.028$) and higher NYHA functional class ($P < 0.001$) and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score ($P = 0.001$) than ARAD patients without HF. Also, ARAD patients with HF had significantly lower LV ejection fraction ($P = 0.003$) and e' -velocity ($P = 0.003$) and higher E/e' ratio ($P = 0.001$), left atrial volume index (LAVI) ($P = 0.046$), LV end-diastolic volume (LVEDV) ($P = 0.001$), LV end-systolic volume (LVESV) ($P = 0.001$), and LV mass index ($P = 0.009$) than ARAD patients without HF. All procedures were successful. In contrast to blood pressure and renal function, there was a significant interaction in E/e' ($P_{\text{interaction}} < 0.001$) between time and HF, and ARAD patients with HF showed a significant ($P < 0.001$) decrease in E/e' albeit those without HF. By the same token, there was a significant interaction in NYHA class ($P_{\text{interaction}} < 0.001$), MLHFQ score ($P_{\text{interaction}} = 0.018$), E -velocity ($P_{\text{interaction}} = 0.002$), LAVI ($P_{\text{interaction}} = 0.001$), LVEDV ($P_{\text{interaction}} = 0.003$), and LVESV ($P_{\text{interaction}} = 0.001$) between time and HF with a significant improvement in all these variables in ARAD patients with HF (NYHA class, $P = 0.001$; MLHFQ score, $P = 0.002$; E -velocity, $P = 0.005$; LAVI, $P = 0.001$; LVEDV, $P = 0.017$; and LVESV, $P = 0.011$).

Conclusions Change in LV filling pressure after renal stenting differed between ARAD patients with and without HF, with a significant improvement in LV filling pressure in patients with HF-ARAD. These unique findings might support clinical cardiac benefits of renal stenting in ARAD patients with HF.

Keywords Heart; Kidney; Failure; Stent; Revascularization

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Introduction

The kidney receives almost 20% of the blood pumped by the heart.¹ Atherosclerotic renal artery disease (ARAD) is a major atherosclerotic disease that affects the kidneys. It presents with a broad spectrum of clinical features, including heart failure (HF), hypertension, and renal failure. Consensus-derived guidelines recommend renal artery stenting to treat patients with ARAD and HF (HF-ARAD patients).^{2,3} Therefore, it might be a prime time to address cardiac function before and after renal artery stenting. Recently, increasing attention is being paid to left ventricular (LV) filling pressure in the pathophysiology of HF-ARAD.^{4–9} The aim of this study was to verify our hypothesis that changes in E/e' , an echocardiographic correlate of LV filling pressure,^{10,11} following renal artery stenting may differ between ARAD patients with and without HF.

Methods

Patient population

The CARMEL (Cardiac Benefits of Renal Artery Stenting: A Prospective Multicenter Observational) study is a prospective multi-centre observational cohort study of patients with *de novo* symptomatic ARAD who underwent renal artery stenting between September 2012 and December 2015 at 14 institutions in Japan. Informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Renal artery revascularization was indicated for the control of hypertension, renal failure, or HF with reference to previous guidelines.^{2,3} In this study, patients were eligible if they had the following conditions: (i) age ≥ 40 years, (ii) $>50\%$ atherosclerotic renal artery stenosis (in cases of intermediate stenosis, renal artery peak systolic velocity >219 cm/s on duplex ultrasonography or translesional pressure gradient of ≥ 20 mmHg with a pressure wire was confirmed on the basis of the treating physician's discretion),¹² and (iii) reference vessel diameter of 4–6 mm and lesion length ≤ 18 mm. In addition, patients were not eligible if they had the following conditions: (i) chronic renal artery occlusion, (ii) chronic atrial fibrillation, (iii) severe mitral valve disease, or lesions involving (iv) severe calcification, (v) a bifurcation, (vi) thrombosis, or (vii) a renal aneurysm.

The diagnosis of HF was made on the basis of criteria in the Framingham study.¹³ ARAD patients with New York

Heart Association (NYHA) Functional Class 2 and more, or a history of HF hospitalization, were classified as HF-ARAD patients, and others were classified as non-HF-ARAD patients.

Stent procedure

Renal artery stenting was performed with the Palmaz Genesis stent (Cordis, Milpitas, CA, USA) using standard procedures. The route of vascular access, choice of stent size, and use of pre-dilatation or post-dilatation and distal protection were left to the treating physician's discretion. Technical success was defined as residual stenosis less than 30%. Patients received dual anti-platelet therapy before the procedure and an anti-platelet regimen after the procedure, but this was also left to the discretion of the attending physician. In patients with renal failure, intravenous fluid therapy before and after the procedure was considered for the prevention of contrast-induced nephropathy.

Clinical, renal ultrasonographic, and echocardiographic parameters

Data on study patients were prospectively collected at each institution before renal artery stenting, as well as on the following day and at 1 month and 6 month follow-up. As part of routine clinical practice, clinical data including blood pressure, number of anti-hypertensive agents, estimated glomerular filtration rate (eGFR), NYHA functional class, and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score were recorded. Echocardiographic data included LV ejection fraction (LVEF), peak early diastolic mitral inflow velocity (E-velocity), peak early diastolic mitral annular velocity in the septum (e' -velocity), E/e' ratio, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), left atrial volume index (LAVI), and LV mass index (LVMI). Left atrial volume and LVEF were measured by the Simpson method. LAVI was calculated as left atrial volume/body surface area. LV mass (LVM) was calculated using the modified Devereux formula.¹⁴ LVMI was calculated as LVM/body surface area. Body surface area was calculated using the formula of Du Bois and Du Bois.¹⁵ Renal ultrasonographic data included peak systolic velocity (PSV) in the renal artery, pole-to-pole length in the kidney, and resistive index (RI) in the kidney that was calculated with the following formula: (peak systolic velocity – end diastolic velocity)/peak systolic velocity.

Core laboratory analysis of angiographic and echocardiographic data

Angiographic data were sent to an independent angiographic core laboratory at Stanford University for quantitative vessel analysis. Echocardiographic data evaluated at each institution were sent to an independent echocardiographic core laboratory at Kawasaki Medical School to be assessed and approved by experienced physicians.

Study endpoints

The primary endpoint was the difference in the change in E/e' before and after renal artery stenting between patients with and without HF. The secondary endpoints were the difference in E-velocity, e' -velocity, blood pressure, number of anti-hypertensive agents, eGFR, NYHA functional class, MLHFQ score, re-hospitalization due to HF, re-intervention for in-stent restenosis, and major adverse cardiovascular events (death, myocardial infarction, stroke, and renal event).

Statistical analysis

On the basis of previous studies,^{4,5} 30 patients (15 patients in each group) were required to detect the primary endpoint with a power of 80% and a significance level of 5%. The ratio of non-HF patients to HF patients in clinical practice was estimated to be approximately 3.0. Allowing for 10% dropout, a total sample size of 66 patients was required for this study. G*POWER version 3.1.9.2 (Heinrich Heine University, Düsseldorf, Germany) was performed for sample size estimation.

Data are expressed as means \pm standard deviation or numbers and percentages. Categorical data were compared using the χ^2 test or Fisher's exact test as appropriate. Differences between the two independent groups were evaluated with Student's *t*-test or Welch's *t*-test for parametric continuous variables or the Mann-Whitney *U* test for non-parametric continuous variables. Distributions of continuous variables were determined using the Kolmogorov-Smirnov test. Repeated measurements were analysed using a mixed model including subjects as random factor, and time point, the presence of HF, and interaction between time point and the presence of HF. An unstructured covariance matrix was assumed. $P < 0.05$ was considered significant. SPSS version 22 (IBM Corp., Armonk, NY, USA) was used for all analyses.

Results

Baseline characteristics

Initially, 82 patients were enrolled in this study. However, six patients were excluded from the final analysis because of atrial fibrillation ($n = 4$) or severe mitral valve disease ($n = 2$) identified by the core laboratory. As a result, 76 patients were included in the final analysis. Sixty-two patients (82%) had unilateral ARAD, and 14 (18%) had bilateral ARAD. The baseline clinical and echocardiographic characteristics of the subjects are shown in *Table 1*. LVEF $< 50\%$ was observed in 28% of patients and $E/e' > 15$ in 38%. A breakdown of medication such as anti-hypertensive agent and diuretic was as follows: calcium channel blocker in 80%, angiotensin-converting enzyme inhibitor in 9%, angiotensin II receptor blocker in 74%, renin inhibitor in 3%, alpha-blocker in 11%, beta-blocker in 41%, alpha-beta-blocker in 20%, and diuretic in 37%.

Characteristics of patients with and without heart failure

Thirty-nine per cent (30 patients) were HF-ARAD, and 61% (46 patients) were non-HF-ARAD. HF-ARAD patients had significantly lower eGFR and higher NYHA functional class and MLHFQ score than non-HF-ARAD patients. Also, HF-ARAD patients had significantly lower LVEF and e' -velocity and higher E/e' ratio, LAVI, LVEDV, LVESV, and LVMI than non-HF-ARAD patients (*Table 1*).

As for renal ultrasonographic parameters, PSV was significantly higher in the target kidneys compared with non-target kidneys whether HF-ARAD patients or non-HF-ARAD patients. Of great note, both RI and pole-to-pole kidney length were significantly higher in the non-target kidneys compared with the target kidneys in HF-ARAD patients (*Table 2*).

Outcomes of renal artery stenting

The 76 subjects underwent stenting procedures in 90 renal arteries, in all of which technical success was achieved without significant complication. Lesion length was 11.9 ± 3.6 mm, and reference vessel diameter was 5.2 ± 0.9 mm. Per cent of diameter stenosis significantly ($P < 0.001$) decreased from 64.2 ± 16.3 to $11.8 \pm 6.8\%$, and minimum lumen diameter significantly ($P < 0.001$) increased from 1.9 ± 0.8 to 4.8 ± 0.7 mm. PSV in the target renal artery significantly ($P < 0.001$) decreased from 290 ± 116 to 93 ± 42 cm/s after renal artery stenting.

There were no cardiac events, renal events, or deaths; one patient experienced an ischaemic stroke on the day after the procedure. During follow-up, although one patient died from

Table 1 Clinical and echocardiographic characteristics

Variable	Overall <i>n</i> = 76	Heart failure (+) <i>n</i> = 30	Heart failure (-) <i>n</i> = 46	<i>P</i> value
Clinical variable				
Age (years)	73 ± 9	74 ± 9	72 ± 10	0.275
Male, <i>n</i> (%)	56 (74)	24 (80)	32 (70)	0.313
Unilateral/bilateral, <i>n</i> (%)	62 (82)/14 (18)	22 (73)/8 (27)	40 (87)/6 (13)	0.134
Hypertension, <i>n</i> (%)	73 (96)	29 (97)	44 (96)	1
Resistant hypertension (≥3 medications), <i>n</i> (%)	45 (59)	21 (70)	24 (52)	0.122
Dyslipidaemia, <i>n</i> (%)	55 (72)	24 (80)	31 (67)	0.23
Diabetes mellitus, <i>n</i> (%)	38 (50)	11 (37)	27 (59)	0.06
Smoking history, <i>n</i> (%)	40 (53)	16 (53)	24 (52)	0.921
Systolic blood pressure (mmHg)	142 ± 20	143 ± 21	141 ± 20	0.64
Diastolic blood pressure (mmHg)	73 ± 14	76 ± 16	72 ± 13	0.185
Number of anti-hypertensive agents	2.8 ± 1.0	2.8 ± 0.9	2.8 ± 1.1	0.566
eGFR (mL/min/1.73 m ²)	44 ± 20	38 ± 17	49 ± 21	0.028
NYHA functional class	1.5 ± 0.8	2.3 ± 0.9	1	<0.001
MLHFQ score	25 ± 22	36 ± 24	18 ± 17	0.001
Renin (ng/mL/h)	8.8 ± 12.8	10.9 ± 16.2	7.3 ± 9.5	0.74
Echocardiographic variable				
Heart rate (b.p.m.)	68 ± 12	67 ± 11	68 ± 13	0.638
Left ventricular ejection fraction (%)	57 ± 12	51 ± 15	61 ± 9	0.003
Left ventricular ejection fraction <50%, <i>n</i> (%)	21 (28)	13 (43)	8 (17)	0.013
E-velocity (cm/s)	68 ± 21	73 ± 26	64 ± 15	0.137
E/e' ratio	15.4 ± 5.6	17.8 ± 5.8	13.7 ± 4.9	0.001
e'-velocity (cm/s)	4.7 ± 1.5	4.2 ± 1.0	5.1 ± 1.6	0.003
Left atrial volume index (mL/m ²)	38 ± 15	43 ± 17	35 ± 13	0.046
Left ventricular end-diastolic volume (mL)	89 ± 42	110 ± 47	76 ± 32	0.001
Left ventricular end-systolic volume (mL)	40 ± 28	55 ± 36	31 ± 16	0.001
Left ventricular mass index (g/m ²)	117 ± 31	128 ± 33	109 ± 28	0.009

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire. *P* value: heart failure (+) vs. (-).

Table 2 Renal ultrasonographic characteristics

Variable	Target kidney <i>n</i> = 90	Non-target kidney <i>n</i> = 62	<i>P</i> value
Peak systolic velocity in the renal artery (cm/s)			
Heart failure	284 ± 138	126 ± 62	<0.001
Non-heart failure	293 ± 100	131 ± 71	<0.001
Pole-to-pole kidney length (cm)			
Heart failure	9.6 ± 1.1	10.3 ± 0.6	0.007
Non-heart failure	9.7 ± 1.3	9.7 ± 1.1	0.905
Resistive index in the kidney			
Heart failure	0.67 ± 0.13	0.76 ± 0.08	0.014
Non-heart failure	0.73 ± 0.14	0.75 ± 0.11	0.584

an unrelated cause and two patients underwent clinically driven re-intervention, no re-hospitalization due to HF was observed.

Changes of parameters after renal artery stenting

Changes in clinical and echocardiographic variables after renal artery stenting in ARAD patients overall are shown in *Table 3*. Clinically, blood pressure, number of anti-hypertensive agents, NYHA functional class, and MLHFQ score significantly decreased after renal artery stenting.

Frequency of each anti-hypertensive agent and diuretic did not significantly change. With respect to echocardiographic findings, LAVI (*P* = 0.001) and LVESV significantly (*P* = 0.046) decreased, and E/e' and LVMI showed only a trend level of significance (*P* = 0.065 and 0.097), not a significant change.

Changes in clinical and echocardiographic variables in patients with and without HF are shown in *Table 4*. Frequency of each anti-hypertensive agent and diuretic did not significantly change both in patients with and without HF. In contrast to blood pressure, number of anti-hypertensive agents, and eGFR, E/e' showed a significant interaction (*P*_{interaction} < 0.001) between time and HF, suggesting a

Table 3 Changes of clinical and echocardiographic variables

Variable	Baseline	1 day	1 month	6 months	P value
Clinical variable					
Systolic blood pressure (mmHg)	142 ± 20	133 ± 20**	132 ± 18**	137 ± 20	0.002
Diastolic blood pressure, mmHg	73 ± 14	70 ± 12	71 ± 12	75 ± 12	0.027
Number of anti-hypertensive agents	2.8 ± 1	2.6 ± 1.1	2.5 ± 1.2**	2.5 ± 1.2*	0.007
eGFR (mL/min/1.73 m ²)	44 ± 20	46 ± 16	46 ± 17	47 ± 18	0.642
NYHA functional class	1.5 ± 0.8	1.3 ± 0.5	1.2 ± 0.5*	1.2 ± 0.4*	0.017
MLHFQ score	25 ± 22	22 ± 20	18 ± 20*	14 ± 16***	<0.001
Echocardiographic variable					
Heart rate (b.p.m.)	68 ± 12	66 ± 10	67 ± 12	69 ± 14	0.085
Left ventricular ejection fraction (%)	57 ± 12	59 ± 11	59 ± 10	58 ± 11	0.142
E-velocity (cm/s)	68 ± 21	65 ± 21	64 ± 18	64 ± 20	0.296
E/e' ratio	15.4 ± 5.6	14.5 ± 5.5	13.8 ± 4.3*	14.0 ± 5.4	0.065
e'-velocity (cm/s)	4.7 ± 1.5	4.9 ± 2.1	4.9 ± 1.6	5.0 ± 1.7	0.49
Left atrial volume index (mL/m ²)	37.9 ± 15.1	37.3 ± 15.8*	36.1 ± 14.9**	35.4 ± 15.2*	0.001
Left ventricular end-diastolic volume (mL)	89.3 ± 41.9	84.3 ± 31.7	85.4 ± 34.3	86.2 ± 31.2	0.219
Left ventricular end-systolic volume (mL)	40.2 ± 28.1	37.1 ± 22.0	35.8 ± 20.4*	36.8 ± 20.1	0.046
Left ventricular mass index (g/m ²)	117 ± 31	115 ± 32	114 ± 29	109 ± 30	0.097

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

* $P < 0.05$ vs. baseline.

** $P < 0.01$ vs. baseline.

*** $P < 0.001$ vs. baseline.

significant difference in change in E/e' after renal artery stenting between patients with and without HF. HF-ARAD patients showed a significant decrease in E/e' ($P < 0.001$), whereas E/e' remained unchanged in non-HF-ARAD patients ($P = 0.196$). In the *post hoc* analysis, E/e' significantly decreased on the following day ($P = 0.003$) and at 1 month ($P = 0.003$) but not at 6 months in HF-ARAD patients. By the same token, there was a significant interaction in NYHA functional class ($P_{\text{interaction}} < 0.001$), MLHFQ score ($P_{\text{interaction}} = 0.018$), E-velocity ($P_{\text{interaction}} = 0.002$), LAVI ($P_{\text{interaction}} = 0.001$), LVEDV ($P_{\text{interaction}} = 0.003$), and LVESV ($P_{\text{interaction}} = 0.001$) between time and HF, suggesting a significant difference in changes over time between patients with and without HF. Also, all of these variables in HF-ARAD patients significantly decreased after renal artery stenting (NYHA class, $P = 0.001$; MLHFQ score, $P = 0.002$; E-velocity, $P = 0.005$; LAVI, $P = 0.001$; LVEDV, $P = 0.017$; and LVESV, $P = 0.011$). Even in the *post hoc* analysis, significant improvement in both NYHA functional class and MLHFQ score was sustained up to 6 months. In contrast, LVMI showed no significant interaction between time and HF.

Discussion

The main findings of this study were as follows: (i) HF-ARAD patients presented with not only lower quality of life but also more severe systolic–diastolic LV dysfunction and renal failure than non-HF-ARAD patients; (ii) changes in E/e' after renal artery stenting showed a significant difference between ARAD patients with and without HF, and E/e' improved significantly after renal artery stenting in ARAD patients with HF but not in those without HF; and (iii) in parallel with E/e',

changes in NYHA functional class, MLHFQ score, E-velocity, LAVI, LVEDV, and LVESV showed significant differences between ARAD patients with and without HF, and these variables improved significantly after renal artery stenting in HF-ARAD patients.

According to previous studies,^{16–19} ARAD adversely affected the heart, increasing the probability of developing LV hypertrophy and increased LV mass compared with individuals without ARAD. Given the recently published criteria of diastolic dysfunction (annular e'-velocity < 7 cm/s, septal E/e' ratio > 15 , and LAVI > 34 mL/m²),²⁰ the present study demonstrated that ARAD patients overall can be characterized by diastolic dysfunction, as shown in *Table 1*. Furthermore, the present study found that HF-ARAD patients had not only lower eGFR but also higher E/e', LAVI, LVEDV, LVESV, and LVMI and lower LVEF and e'-velocity than non-HF-ARAD patients. These findings suggest that ARAD patients with HF are complicated by more severe systolic–diastolic dysfunction and renal failure than those without HF. Also, as shown in *Table 2*, in HF-ARAD patients, both RI and pole-to-pole length in the kidney were significantly higher in the non-target kidneys compared with the target kidney. This asymmetric paradox suggests the preserved parenchyma in the kidney with ARAD and the parenchymal disorder in the potentially compensatory hypertrophied kidney without ARAD due to the direct exposure to hypertension. These findings support the preceding hypothesis that pathophysiological mechanisms underlying HF-ARAD include sodium and fluid retention by co-existent cardiorenal disorder and the failure of compensatory pressure natriuresis.^{2,8}

With respect to treatment of HF-ARAD patients, since the first report about cardiac load reduction immediately after renal artery revascularization approximately three decades ago,^{21,22} case reports and retrospective studies have shown

Table 4 Differences in changes of clinical and echocardiographic variables between patients with and without heart failure

Variable	Heart failure	Baseline	1 day	1 month	6 months	P value	P for interaction between time and heart failure
Clinical variable							
Systolic blood pressure (mmHg)	+	143 ± 21	133 ± 22	130 ± 19	140 ± 22	0.023	0.449
	-	141 ± 20	133 ± 20	133 ± 17	136 ± 19	0.049	
Diastolic blood pressure (mmHg)	+	76 ± 16	69 ± 13	70 ± 15	74 ± 12	0.046	0.331
	-	72 ± 13	70 ± 12	72 ± 10	75 ± 13	0.381	
Number of anti-hypertensive agents	+	2.8 ± 0.9	2.5 ± 1.0	2.3 ± 1.2*	2.6 ± 1.0	0.041	0.108
	-	2.8 ± 1.1	2.7 ± 1.2	2.6 ± 1.1	2.5 ± 1.3	0.127	
eGFR (mL/min/1.73 m ²)	+	38 ± 17	41 ± 17	43 ± 17	43 ± 17	0.175	0.635
	-	49 ± 21	49 ± 16	49 ± 16	49 ± 18	0.991	
NYHA functional class	+	2.3 ± 0.9	1.6 ± 0.6**	1.4 ± 0.6**	1.4 ± 0.5**	0.001	<0.001
	-	1	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.419	
MLHFQ score	+	36 ± 24	30 ± 22	24 ± 22	17 ± 17**	0.002	0.018
	-	18 ± 17	16 ± 15	14 ± 18	12 ± 16	0.07	
Echocardiographic variable							
Heart rate (b.p.m.)	+	67 ± 11	64 ± 9	67 ± 11	70 ± 15	0.246	0.819
	-	68 ± 13	66 ± 11	67 ± 13	69 ± 13	0.427	
Left ventricular ejection fraction (%)	+	51 ± 15	54 ± 12	56 ± 11	55 ± 12	0.104	0.13
	-	61 ± 9	61 ± 9	61 ± 8	61 ± 10	0.47	
E-velocity (cm/s)	+	73 ± 26	62 ± 24**	61 ± 21*	63 ± 22	0.005	0.002
	-	64 ± 15	67 ± 19	65 ± 16	65 ± 19	0.581	
E/e' ratio	+	17.8 ± 5.8	15.2 ± 5.4**	14.3 ± 4.4**	16.0 ± 5.2	<0.001	<0.001
	-	13.7 ± 4.9	14.1 ± 5.6	13.5 ± 4.2	12.6 ± 5.2	0.196	
e' velocity (cm/s)	+	4.2 ± 1.0	4.2 ± 1.2	4.5 ± 1.5	4.1 ± 1.3	0.432	0.154
	-	5.1 ± 1.6	5.4 ± 2.5	5.2 ± 1.6	5.6 ± 1.8	0.258	
Left atrial volume index (mL/m ²)	+	43 ± 17	41 ± 19**	38 ± 17**	39 ± 18**	0.001	0.001
	-	35 ± 13	35 ± 12	35 ± 13	33 ± 13	0.508	
Left ventricular end-diastolic volume (mL)	+	110 ± 47	99 ± 35	94 ± 42*	98 ± 35	0.017	0.003
	-	76 ± 32	74 ± 25	80 ± 28	77 ± 25	0.265	
Left ventricular end-systolic volume (mL)	+	55 ± 36	49 ± 27	44 ± 26*	47 ± 24	0.011	0.001
	-	31 ± 17	29 ± 14	31 ± 14	30 ± 12	0.583	
Left ventricular mass index (g/m ²)	+	128 ± 33	129 ± 34	125 ± 29	121 ± 33	0.609	0.412
	-	109 ± 28	105 ± 27	106 ± 27	101 ± 26*	0.044	

eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

*P < 0.05 vs. baseline.

**P < 0.01 vs. baseline.

certain improvement of HF after renal artery revascularization, reflecting the transition of treatment from surgery to angioplasty and stenting.²³ Previous retrospective studies regarding renal artery stenting reported that HF-ARAD patients had clinical benefits such as downgraded NYHA functional class, no recurrence of HF, decrease in the number and proportion of re-hospitalization, and increased time to re-hospitalization after renal artery revascularization.^{4,24–26} More recent prospective observational studies reported that renal artery revascularization was associated with a substantial reduction in mortality in HF-ARAD patients.^{27,28} Given these clinical cardiac benefits that HF-ARAD patients received, the present study addressed cardiac function responses to renal artery stenting using echocardiography.

Recently, there is increasing attention to LV filling pressure or E/e' on echocardiography in ARAD patients.^{5–7,29,30} However, the effects of renal artery stenting on E/e' in HF-ARAD patients remain controversial. In this study, as shown in *Table 3*, ARAD patients overall did not show a significant improvement in E/e' . However, as shown in *Table 4*, despite no significant difference in changes of blood pressure, number of anti-hypertensive agents, and eGFR, the changes of E/e' after renal artery stenting differed significantly between ARAD patients with and without HF, and E/e' in HF-ARAD patients showed a significant improvement overtime. In parallel with E/e' , there were significant differences in changes of NYHA functional class, MLHFQ, E-velocity, LAVI, LVEDV, and LVESV after renal artery stenting between ARAD patients with and without HF, and all of these variables significantly improved after renal artery stenting in HF-ARAD patients. These findings can support the previous studies using echocardiography and cardiac MR in which HF-ARAD patients could experience a decrease in LV filling pressure, LVEDV, and LVESV as well as an improvement in cardiac symptoms after renal artery stenting.^{5–7,31} In the *post hoc* analysis of HF-ARAD patients, an improvement in E/e' was significant even on the following day and at 1 month but not at 6 months. These findings suggest that renal artery stenting is a remedy to quickly attenuate the vicious cardiorenal cycle triggered by ARAD and stabilize HF and support the preceding hypothesis that renal artery revascularization would facilitate to reduce the intravascular volume and prevent the fluid retention by allowing pressure natriuresis in the treated kidney.²³ A subsequent rise in E/e' at 6 months in HF-ARAD patients might be affected by the pre-existing more severe cardiorenal disorders. On the other hand, as shown in the change of NYHA functional class and MLHFQ score, it is noteworthy that significant improvement in both symptom and quality of life in HF-ARAD patients was maintained even up to 6 month follow-up. These findings suggest that the clinical cardiac benefits could be sustained overtime even after the shrinkage of echocardiographic improvements.

There has been a controversy over the effects of renal artery revascularization on LV structure since the first

report of a significant reduction of LVMI after renal artery stenting one decade ago.³² According to a single-centre, single-blinded randomized study by Marcantoni *et al.*,³³ incidental ARAD patients with renal artery stenosis >50 to $\leq 80\%$ and ischaemic heart disease could not benefit from renal artery stenting over medical therapy in terms of reduction of LVMI. The cardiac magnetic resonance sub-study of the ASTRAL (Angioplasty and Stenting for Renal Artery Lesions) trial reported no benefits from renal artery stenting on LVM, compared with medical therapy.³⁴ However, according to the most updated meta-analysis of echocardiographic studies including 360 patients,³⁵ renal artery revascularization had a beneficial effect on LV structure. In the present study, ARAD patients without HF showed a significant decrease in LVMI after renal artery stenting whereas ARAD patients overall or ARAD patients with HF did not. Given these findings, LV hypertrophy might be reversible at the early stage of cardiac disorder.

Some limitations of this study should be taken into consideration. First, our sample size was relatively small, which may bring in Type 2 error. Further studies including a larger number of HF-ARAD patients might demonstrate the effects of renal artery stenting on cardiac structure, geometry, and function. Second, because the follow-up period of this study was 6 months, long-term cardiac effects still remain unclear. In particular, multi-factorial disorders might affect cardiac function adversely in patients with ARAD. Third, apart from the number of anti-hypertensive agents, medical therapy was individualized at the discretion of each attending physician, which might have affected clinical and echocardiographic outcomes. Fourth, although we employed a core laboratory-based analysis, the potentially disparate quality of echocardiographic evaluation might have also affected the outcomes. Finally, this study excluded patients with atrial fibrillation and severe mitral valve disease, although these disorders might be contaminated in the clinical practice.

In conclusion, change in LV filling pressure after renal artery stenting differed between ARAD patients with and without HF, with a significant improvement in LV filling pressure in patients with HF-ARAD. These unique findings might support clinical cardiac benefits of renal artery stenting in ARAD patients with HF.

Conflict of interest

None declared.

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