



Clinical Implications of Intrarenal Hemodynamic Evaluation by Doppler Ultrasonography in Heart Failure

Noriko Iida, BA,^a Yoshihiro Seo, MD,^b Seika Sai, MD,^b Tomoko Machino-Ohtsuka, MD,^b Masayoshi Yamamoto, MD,^b Tomoko Ishizu, MD,^{b,c} Yasushi Kawakami, MD,^c Kazutaka Aonuma, MD^b

ABSTRACT

OBJECTIVES This study clarified the characteristics of intrarenal Doppler ultrasonography (IRD) profiles and their prognostic implications in heart failure (HF).

BACKGROUND IRD can assess intrarenal hemodynamics.

METHODS Initially, 224 patients with HF were prospectively enrolled; 151 inpatients were enrolled during hospitalization for HF, and 73 were outpatients in our institution. In IRD profiles of interlobar vessels, the arterial resistance index (RI), venous impedance index (VII), and intrarenal venous flow (IRVF) pattern were assessed. Patients were followed to evaluate the associations with 1-year prognosis. Primary endpoints included death from cardiovascular disease and unplanned hospitalization for HF.

RESULTS Finally, 217 patients with adequate IRD images were enrolled. IRD profiles were associated with conventional risk factors for HF. In particular, IRVF was associated with mean right atrial pressure (RAP); 3 IRVF patterns were stratified by RAP (in a continuous pattern: 5.4 ± 2.5 ; in a biphasic pattern: 9.5 ± 3.5 ; and in a monophasic pattern: 14.9 ± 4.3 mm Hg; $p < 0.001$). In addition, the monophasic IRVF pattern had a poorer prognosis than the other patterns (log rank $p < 0.001$), and prognosis was poorer for the biphasic pattern than for the continuous flow pattern (log rank $p = 0.01$). Multivariate Cox proportional hazard model analysis revealed that IRVF patterns were associated with the endpoints, independent of other HF risk factors.

CONCLUSIONS IRVF patterns, rather than RI, depended on RAP, suggesting a correlation with renal congestion. In addition, IRVF patterns strongly correlated with clinical outcomes independent of RAP and other risk factors and might provide additional information to stratify vulnerable HF patients. (J Am Coll Cardiol HF 2016;4:674-82)
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Cardiorenal syndrome has been widely recognized as important in the pathophysiology of heart failure (HF). Renal impairment is commonly observed and associated with adverse clinical outcomes in patients with HF (1-3). Renal congestion caused by increased central venous pressure (CVP) has been one of the main pathophysiologic findings in cardiorenal syndrome (4,5). However, CVP is a surrogate for renal congestion in HF, and intrarenal hemodynamics have not been well studied in the assessment of renal congestion.

Renal congestion occurs mainly in renal parenchymal regions, accompanied by increased renal interstitial pressure (6). Altered parenchymal conditions may directly compress vessels in the renal parenchymal regions or reduce compliance of vessels, accompanied by increased CVP as resistances. As a result, changes in vessel shape and function will affect vessel flow. Intrarenal Doppler ultrasonography (IRD) has been used to evaluate intrarenal hemodynamics. The resistance index (RI) of the renal artery is widely used in assessing renal function,

From the ^aClinical Laboratory, University of Tsukuba Hospital, Tsukuba, Japan; ^bCardiovascular Division, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; and the ^cDepartment of Clinical Laboratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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pathophysiology, and prognosis in both renal and cardiac disease (7-13). In addition, intrarenal venous flow (IRVF) also can be visualized and has been studied mainly in assessment of urological diseases (14-17). Because IRVF depends on surrounding renal parenchymal histology as much as on right atrial function, the IRVF profile may be associated with renal congestion (15,16). To the best of our knowledge, IRD profiles have not been well studied in patients with HF, although cardiorenal interactions have been the focus of recent research. We therefore hypothesized that the IRD profile of both intrarenal arterial and venous flow may be altered by accompanying changes in parenchymal conditions related to renal congestion in patients with HF. The aims of this study were to clarify the determinants associated with IRD profiles in HF and to evaluate the prognostic implications of the IRD profiles.

SEE PAGE 683

METHODS

STUDY DESIGN. Initially, 224 patients with HF were prospectively enrolled from December 2012 to November 2014; 151 inpatients were enrolled during hospitalization for HF, and 73 were outpatients in our institution. IRD studies in this cohort were performed when the condition of the patients was stable before discharge or in the outpatient clinic.

Among the inpatients, 103 underwent right heart catheterization for assessment of cardiovascular disease and also underwent IRD studies within 24 h before catheterization. In addition, 38 normal subjects without cardiovascular disease, hypertension, or diabetes were enrolled to determine the normal IRD profile. Ethical approval was obtained from the local institutional review committee, and all patients provided written informed consent.

IRD STUDY. IRD studies were followed by comprehensive echocardiographic examinations using a Vivid E9 system (GE Healthcare, Horton, Norway) with a sector transducer frequency range of 2.5 to 5 MHz. IRD was recorded in the right kidney with the patient in the left lateral decubitus position. The velocity range of the color Doppler was set to approximately 16 cm/s. Color Doppler images were used to determine interlobar vessels, and the sample volume was set based on the color Doppler signals derived from interlobar arteries (Figure 1). Pulsed Doppler waveforms of the interlobar arteries and veins were recorded simultaneously. The RI at a lobar artery was calculated as the maximum flow velocity minus diastolic flow velocity, divided by maximum flow velocity (7). The venous

impedance index (VII) was calculated as the peak maximum flow velocity minus maximum flow velocity at nadir, divided by peak maximum flow velocity (8). In addition, Doppler waveforms of IRVF were divided into 3 flow patterns: continuous, biphasic discontinuous, and monophasic discontinuous (Figure 1). Discontinuous flow was defined as a pattern in which velocity at the nadir was zero. Therefore, VII was calculated as 1.0 in patients with discontinuous patterns. All measurements were averaged over 3 cardiac cycles during sinus rhythm. In patients with atrial fibrillation, an index beat, which was the beat following 2 preceding cardiac cycles of equal duration, was used for each measurement.

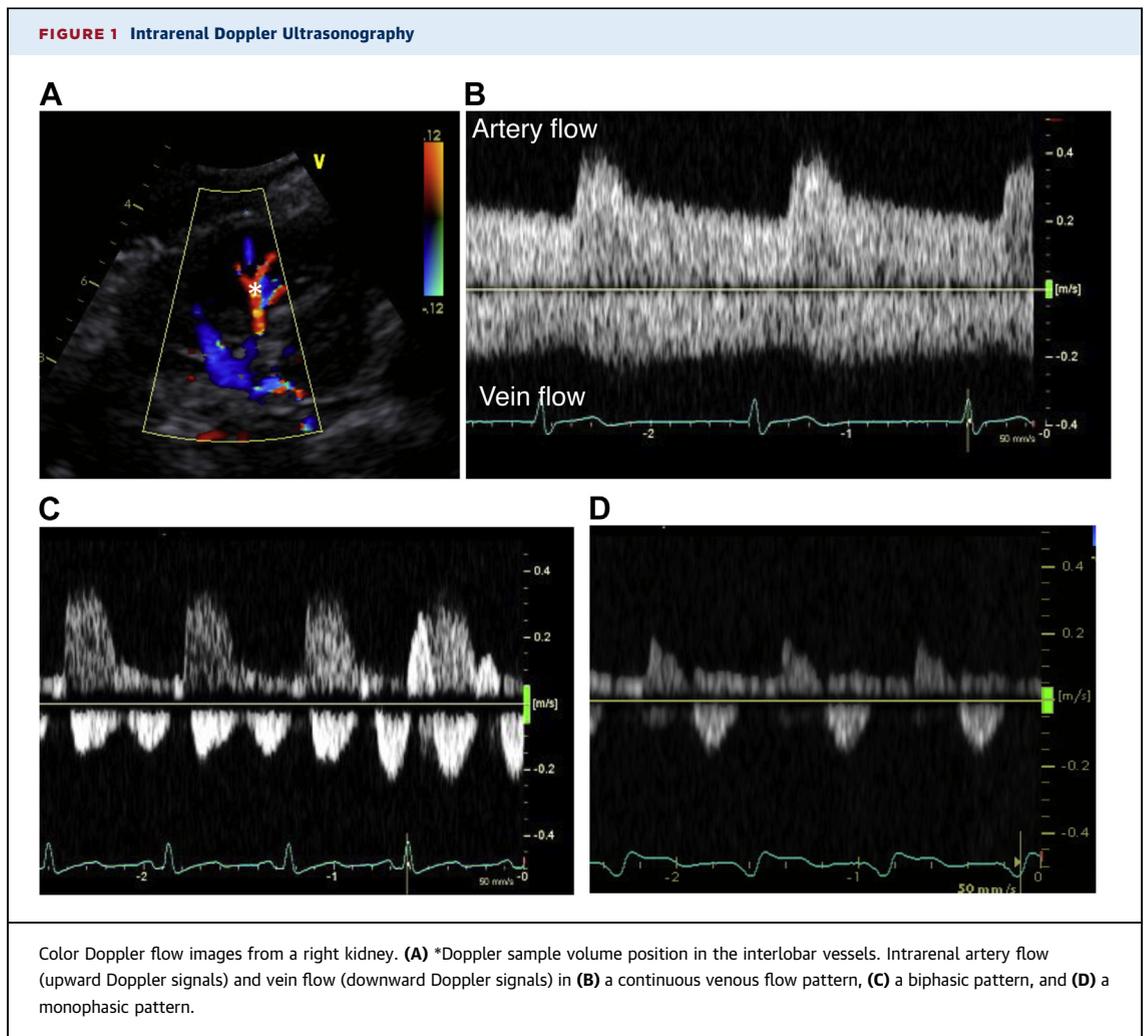
ECHOCARDIOGRAPHY. Comprehensive transthoracic echocardiography was performed according to published guidelines (18). Right ventricular systolic function was assessed by the fractional area change ratio. In patients with tricuspid regurgitation (TR), peak pressure gradients between the right ventricle and right atrium were measured. Degree of TR was evaluated in a comprehensive manner, using all available parameters based on published guidelines (19).

The velocity of flow in the hepatic veins was recorded from the subcostal window; and hepatic vein systolic (HV-S), HV-diastolic (HV-D) flow velocities, and the S/D ratio were measured. With the patient in the supine position, the diameters of the inferior vena cava were measured in the subcostal view at 1.0 to 2.0 cm from the junction with the right atrium. The maximum diameter of the inferior vena cava and the percentage of decrease in the diameter during inspiration were measured. Right atrial pressure (RAP), used as a surrogate of CVP, was estimated using 2 grades consisting of ≤ 10 and > 10 mm Hg, although 3 grade classifications are recommended by the guidelines (20). The reliability of our binary classification is summarized in Online Table 1. In the clinical outcome study, the estimated RAP classification was used only as the surrogate for CVP.

LABORATORY DATA AND RENAL FUNCTION. Peripheral blood samples were taken just before echocardiographic studies. Estimated glomerular filtration rate (eGFR) was calculated according to the isotope dilution mass spectrometry modification of diet in renal disease equation modified for the Japanese population, that is, $eGFR (ml/min/1.73 m^2) = 194 \times (\text{serum creatinine})^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$. Worsening renal function (WRF) was assessed and defined as an increase in serum creatinine of 0.3 mg/dl from baseline to discharge (1-3). Plasma

ABBREVIATIONS AND ACRONYMS

BNP	= brain natriuretic peptide
BUN	= blood urea nitrogen
eGFR	= estimated glomerular filtration rate
HF	= heart failure
IRD	= intrarenal Doppler ultrasonography
IRVF	= intrarenal venous flow
PCWP	= pulmonary capillary wedge pressure
RAP	= right atrial pressure
RI	= resistance index
VII	= venous impedance index



concentration of brain natriuretic peptide (BNP) was measured using a chemiluminescent enzyme immunoassay kit (Lumipulse BNP, Fujirebio Inc., Tokyo, Japan) and an immunoassay system (Lumipulse Presto II; Fujirebio Inc).

CARDIAC CATHETERIZATION. Right heart catheterization was performed with a 7-F balloon-tipped pulmonary artery catheter (Swan-Ganz, Baxter Healthcare, Irvine, California). All pressure data were measured at end expiration, and reported values represent the average of 5 to 10 cardiac cycles. Cardiac index was measured using the thermodilution method. If a patient had pulmonary artery hypertension, congenital heart disease, or significant TR, the cardiac index was measured using the Fick method.

CLINICAL OUTCOME. Clinical outcomes were evaluated for 1 year after discharge or enrollment at our outpatient clinic. Primary endpoints were defined as death from cardiovascular disease or unplanned hospitalization for HF.

REPRODUCIBILITY. Two observers independently assessed RI, VII, and IRVF patterns in 20 patients. To test intraobserver variability, a single observer analyzed the data twice on occasions separated by a 1-month interval. To test interobserver variability, a second observer analyzed data without knowledge of the first observer's measurements. Reproducibility was assessed as the mean percentage of error (absolute difference divided by the mean of the 2 observations).

STATISTICAL ANALYSIS. Results are number (%) or mean \pm SD. Comparisons between 2 groups were performed using the Student *t* test for continuous variables and chi-square test for categorical variables. One-way analysis of variance (ANOVA) with the post-hoc Tukey-Kramer test was used to compare variables between IRVF patterns. Independent determinants of RI ≥ 0.70 , biphasic and monophasic IRVF patterns, were assessed by multivariate logistic regression analyses adjusted for age and sex, using

univariate factors with a value of $p < 0.05$. To avoid overfitting of the multivariate logistic regression models, a step-up procedure based on the likelihood ratio statistic was used, except for the analysis of the biphasic flow pattern. Kaplan-Meier analysis was performed to determine the influence of IRVF patterns on the endpoints. The risk of clinical endpoints was determined with Cox proportional hazard models. Univariate factors with a p value of <0.05 were entered into the multivariate model to assess the effect of the parameters on endpoints. Similarly, a step-up procedure was used in multivariate model analysis. A value of $p < 0.05$ was considered statistically significant. All calculations were performed with SPSS version 22 software (SPSS Inc., Chicago, Illinois).

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS.

Of the 224 patients, 7 patients (3.1%) were excluded because of inadequate IRD images. Finally, 217 patients and 38 normal control subjects were studied (Online Tables 2 and 3). In the control subjects, the 99% confidence interval (CI) of RI ranged from 0.48 to 0.68. Only the continuous IRVF pattern was observed in these subjects, and the 99% CI of VII ranged from 0.14 to 0.52. Thus, $RI \geq 0.70$ and $VII \geq 0.53$ were each considered to indicate abnormal values of RI and VII, and biphasic and monophasic discontinuous flow patterns were considered abnormal IRVF patterns. However, in 105 patients with $VII \geq 0.53$, 101 patients (96.1%) showed VII of 1.0, indicating a discontinuous IRVF pattern. Patients were then classified based on IRVF pattern but not by VII.

DETERMINANTS OF THE IRD PROFILE. Comparisons between characteristics of patients with $RI \geq 0.70$ and those with <0.70 are summarized in Table 1. In the $RI \geq 0.70$ group, patients were older; their hemoglobin (Hb) and eGFR concentrations were significantly lower; their blood urea nitrogen (BUN), BNP, and E/E' (mitral peak velocity of early filling [E]-to-early diastolic mitral annular velocity [E'] ratio) levels were significantly higher; TR was significantly prevalent; and their estimated RAP >10 mm Hg, pulmonary capillary wedge pressure (PCWP), and mean RAP were significantly higher than those in patients with $RI < 0.70$. However, the cardiac indexes did not differ between groups. In a multivariate logistic regression model without catheterization data (model 1), age, Hb, and estimated RAP >10 mm Hg were identified as independent determinants of $RI \geq 0.70$ (Table 2). In a subanalysis model with catheterization data (model 2; $n = 103$), age and

PCWP were selected as the independent determinants. Simple logistic regression analyses are summarized in Online Table 4.

In comparisons of characteristics between IRVF patterns (Table 1), patients with a monophasic pattern were older than those with a biphasic pattern. In patients with a monophasic pattern, BUN, BNP, E/E', PCWP, and mean RAP levels were significantly higher, and eGFR, sodium, and HV-S/D levels were significantly lower than in those with the other 2 patterns. One-half of the patients with a monophasic pattern had E/E' ratio >15 and moderate or severe TR. Most patients with a monophasic pattern used loop diuretics and had an estimated RAP >10 mm Hg. Systolic blood pressure and Hb levels were significantly lower in patients with the monophasic pattern than in those with the continuous pattern. In a comparison between continuous and biphasic patterns, mean RAP was significantly higher in the biphasic pattern. Along with RI, the cardiac index did not differ between the 3 IRVF patterns. Multivariate logistic regression model 1 revealed that estimated RAP >10 mm Hg was significantly associated with the biphasic pattern (Table 2). In a subanalysis of patients who had undergone catheterization, mean RAP only showed a significant but modest association with the biphasic pattern. In contrast, multivariate factors were associated with the monophasic pattern (Online Table 4). In multivariate logistic regression analysis model 1, estimated RAP >10 mm Hg, HV-S/D <0.55 , right ventricular fractional area change, and moderate or severe TR were associated with the monophasic pattern. In model 2, mean RAP was selected as an independent determinant along with HV-S/D <0.55 and sodium level. The prevalence of WRF did not differ between RI classifications or among IRVF patterns.

CLINICAL OUTCOME. During the observation periods (mean: 304 ± 114 days; range: 7 to 365 days), 59 patients (27.1%) met the endpoints, including 14 deaths from cardiovascular disease and 45 unplanned hospitalizations for HF. Comparisons between clinical data of patients with events and those without events are summarized in Online Table 1. Kaplan-Meier estimates of the time to endpoint between IRVF patterns are shown in Figure 2. There were significant differences between IRVF patterns. In addition, Kaplan-Meier estimates between continuous and discontinuous IRVF patterns based on the strata of RAP and HV-S/D criteria each are shown in Figure 3. In each stratum, patients with a discontinuous IRVF pattern had poorer prognosis than those with a continuous IRVF pattern.

TABLE 1 Clinical Characteristics and Echocardiographic and Intrarenal Doppler Ultrasound Data

	Total (N = 217)	RI <0.70 (n = 113)	RI ≥0.70 (n = 104)	p Value	IRVF Continuous (n = 117)	Biphasic (n = 51)	Monophasic (n = 49)	p Value ANOVA
Age, yrs	60 ± 16	56 ± 16	64 ± 15	<0.001	59 ± 15	56 ± 16	64 ± 16†	0.04
Male	126 (58)	69 (61)	57 (55)	0.41	70 (60)	32 (63)	24 (49)	0.32
Body mass index, kg/m ²	23 ± 4.7	23 ± 4.1	22 ± 4.1	0.34	24 ± 4.7	22 ± 2.8	22 ± 3.6	0.27
SBP, mm Hg	113 ± 21	120 ± 19	115 ± 20	0.32	116 ± 21	112 ± 20	106 ± 21†	0.01
Heart rate, beats/min	74 ± 15	74 ± 12	74 ± 13	0.79	73 ± 12	74 ± 12	74 ± 12	0.73
Hypertension	93 (43)	43 (38)	50 (48)	0.17	50 (43)	20 (39)	23 (47)	0.56
Diabetes	63 (29)	30 (27)	33 (32)	0.46	35 (30)	19 (37)	19 (18)	0.11
NYHA functional class III or IV	94 (43)	45 (40)	49 (47)	0.33	38 (33)	23 (45)	33 (67)	<0.001
Cardiac diseases								
CAD	22 (15)	10 (9)	12 (12)	0.51	13 (11)	4 (8)	5 (10)	0.81
NICM	91 (42)	50 (44)	41 (39)	0.49	48 (41)	22 (43)	21 (43)	0.96
Valvular disease	36 (17)	11 (10)	25 (24)	0.006	19 (16)	10 (20)	7 (14)	0.77
VSD/ASD	9 (4)	5 (4)	4 (4)	0.83	5 (4)	4 (8)	0	0.14
PAH	20 (9)	15 (13)	5 (5)	0.04	11 (9)	7 (14)	2 (4)	0.25
HFpEF	64 (30)	33 (29)	31 (30)	0.92	38 (33)	8 (16)	18 (37)	0.04
Laboratory data								
Hemoglobin, g/dl	13 ± 2.3	13 ± 2.3	12 ± 2.2	0.001	13 ± 2.1	13 ± 2.3	12 ± 2.4†	0.001
BUN, mg/dl	22 ± 14	20 ± 12	25 ± 14	0.01	19 ± 9.6	22 ± 17	29 ± 17*	<0.001
eGFR, ml/min/1.73 m ²	64 ± 26	69 ± 25	59 ± 26	0.002	67 ± 22	67 ± 24	55 ± 22*	0.005
Sodium, mEq/l	140 ± 3.4	140 ± 3.1	139 ± 3.8	0.14	141 ± 2.9	140 ± 3.4	138 ± 4.0*	<0.001
BNP, pg/ml	481 ± 753	353 ± 551	620 ± 905	0.009	283 ± 531*	707 ± 646	717 ± 992	<0.001
WRF, n (available case, %)	39 (151, 26)	18 (76, 24)	21 (75, 28)	0.55	19 (88, 22)	10 (34, 29)	10 (29, 34)	0.35
Medications								
ACE-I/ARB	158 (73)	71 (72)	77 (74)	0.70	86 (74)	35 (69)	37 (76)	0.72
Beta-blocker	150 (69)	62 (55)	59 (57)	0.78	67 (57)	30 (59)	24 (49)	0.55
Loop diuretics	136 (63)	54 (48)	57 (55)	0.30	47 (40)	28 (55)	36 (74)	<0.001
Spirolactone	110 (51)	55 (49)	55 (53)	0.38	49 (42)	30 (59)	31 (63)	0.02
Echocardiography								
LVEF, %	49 ± 19	49 ± 18	48 ± 19	0.72	51 ± 17	46 ± 21	44 ± 20	0.07
E/E' >15	77 (36)	32 (22)	45 (43)	<0.001	29 (25)	22 (43)	26 (53)	0.001
RV-FAC, %	42 (19)	36 ± 13	37 ± 14	0.52	40 ± 13*	34 ± 12	29 ± 12	<0.001
Moderate or severe TR	42 (19)	18 (12)	24 (23)	0.03	5 (4)	12 (24)	25 (51)	<0.001
RAP >10 mm Hg	61 (28)	19 (13)	42 (40)	<0.001	4 (3)	18 (35)	39 (80)	<0.001
HV-S/D	1.1 ± 0.8	1.3 ± 0.8	0.9 ± 0.9*	<0.001	1.3 ± 0.6	1.2 ± 1.1	0.3 ± 0.6*	<0.001
Catheterization data								
PCWP, mm Hg	13 ± 7.4	11 ± 6.6	16 ± 7.6	0.003	11 ± 6.4	13 ± 6.7	19 ± 6.4*	<0.001
Mean PAP, mm Hg	26 ± 13	25 ± 13	26 ± 13	0.65	23 ± 9.3*	32 ± 14	31 ± 7.8	0.03
Mean RAP, mm Hg	7.5 ± 4.7	6.6 ± 3.9	8.7 ± 5.3	0.02	5.4 ± 2.5	9.5 ± 3.5†	15 ± 4.3*	<0.001
Cardiac index, l/min/m ²	2.8 ± 0.8	2.8 ± 0.8	2.7 ± 0.7	0.38	2.8 ± 0.8	2.9 ± 0.8	2.7 ± 0.8	0.72

Values are mean ± SD, n (%), or median (interquartile range). **Bold** indicate the characteristics with significant difference between groups. *p < 0.05 vs. others. †p < 0.05 vs. continuous pattern. ‡p < 0.05 vs. biphasic pattern.

ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blocker; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CAD = coronary artery diseases; eGFR = estimated glomerular filtration rate; E/E' = ratio of early diastolic peak velocity of Doppler transmitral flow to early diastolic mitral annular velocity; HFpEF = heart failure with preserved ejection fraction; HV-S/D = ratio of hepatic vein systolic to diastolic flow velocities; IRVF = intrarenal venous flow; LVEF = left ventricular ejection fraction; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RI = resistance index; RV-FAC = right ventricular fractional area change ratio; SBP = systolic blood pressure; TR = tricuspid regurgitation; VSD/ASD = ventricular septal defect/atrial septal defect; WRF = worsening renal function.

Univariate and multivariate Cox proportional hazard model analyses are summarized in **Table 3**. As shown in the multivariate Cox proportional hazard model, biphasic and monophasic flow patterns were associated with the endpoints independently of sodium and BNP levels.

REPRODUCIBILITY. Intra- and interobserver variability of RI and VII measurements were as follows: RI: 3.8 ± 3.4 and $6.5 \pm 4.3\%$, respectively; and VII: 5.6 ± 3.6 and $7.2 \pm 4.4\%$, respectively. Classifications of IRVF patterns were completely consistent between intraobserver and interobserver assessments.

DISCUSSION

The 3 major findings of the present study are as follows. First, the common significant determinant of RI ≥ 0.70 and the discontinuous IRVF pattern was increased RAP level >10 mm Hg but not cardiac index. Second, compared to the biphasic IRVF pattern, the monophasic IRVF pattern was associated with multivariate hemodynamic factors, including significant TR and HV flow and more strongly depended on increased RAP. Third, discontinuous IRVF patterns correlated strongly with clinical outcomes independent of RAP and HV-S/D levels.

IRVF

Unlike the IRD profile on the arterial side, the IRD profile on the venous side has not been the focus in cardiac disease. This study showed that IRVF could be noninvasively assessed with high clinical feasibility and acceptable reproducibility by a conventional echocardiographic system. A few studies have reported changes in IRVF in obstructive uropathy and renal diseases, preeclampsia, and diabetic nephropathy, but CVP and TR were never considered determinants of IRVF (14-17). IRVF profile was altered by increases in RAP, whereas cardiac index was not associated with the IRVF profile. A low-output condition affects intrarenal circulation, but in the present study, the association of cardiac index was not significant, even with RI. Insignificant interaction with inflow suggests 2 possible mechanisms that can alter IRVF patterns: increased CVP as the resistance of IRVF and renal parenchymal congestion accompanied by increased renal interstitial pressure, which reduces intrarenal parenchymal compliance around the intrarenal vessels (6). In addition, significant TR was associated with the monophasic pattern. This finding suggests that increased resistance from significant TR impedes IRVF during systole because flow was usually observed during diastole in the monophasic pattern. Maeder et al. (21) reported the significant contribution of TR to renal dysfunction, probably by elevation of the CVP and renal venous pressure. It is highly likely that renal congestion further emphasized by significant TR contributes to the exacerbation of renal dysfunction. Thus, IRVF in patients with HF would be affected by both central venous hemodynamics and reduced renal parenchymal compliance related to renal congestion.

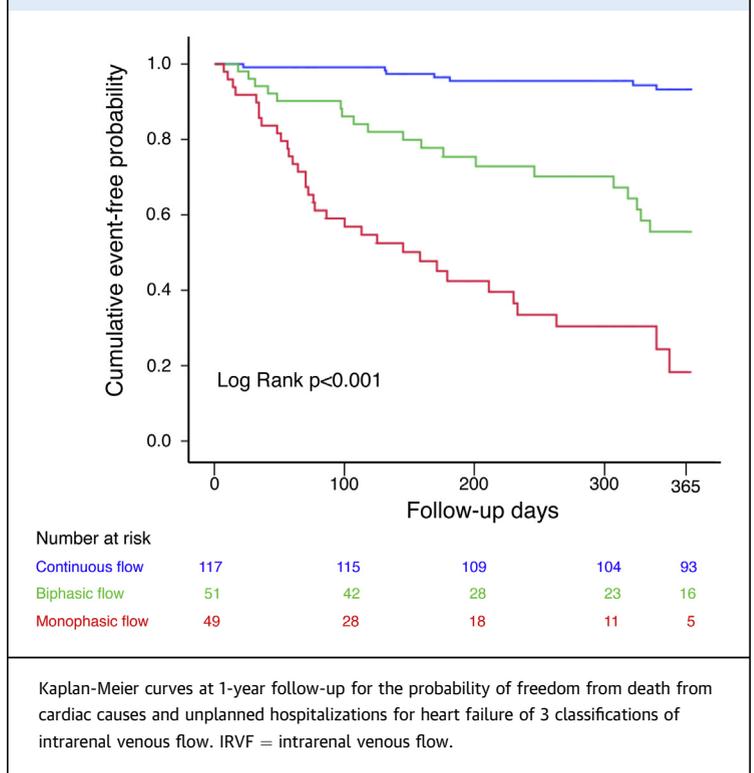
RI IN HF. The role of RI in HF has not been well studied. To our knowledge, only 2 studies reported RI in HF. Ennezat et al. (11) reported that RI was greater in patients with HF and preserved ejection fraction

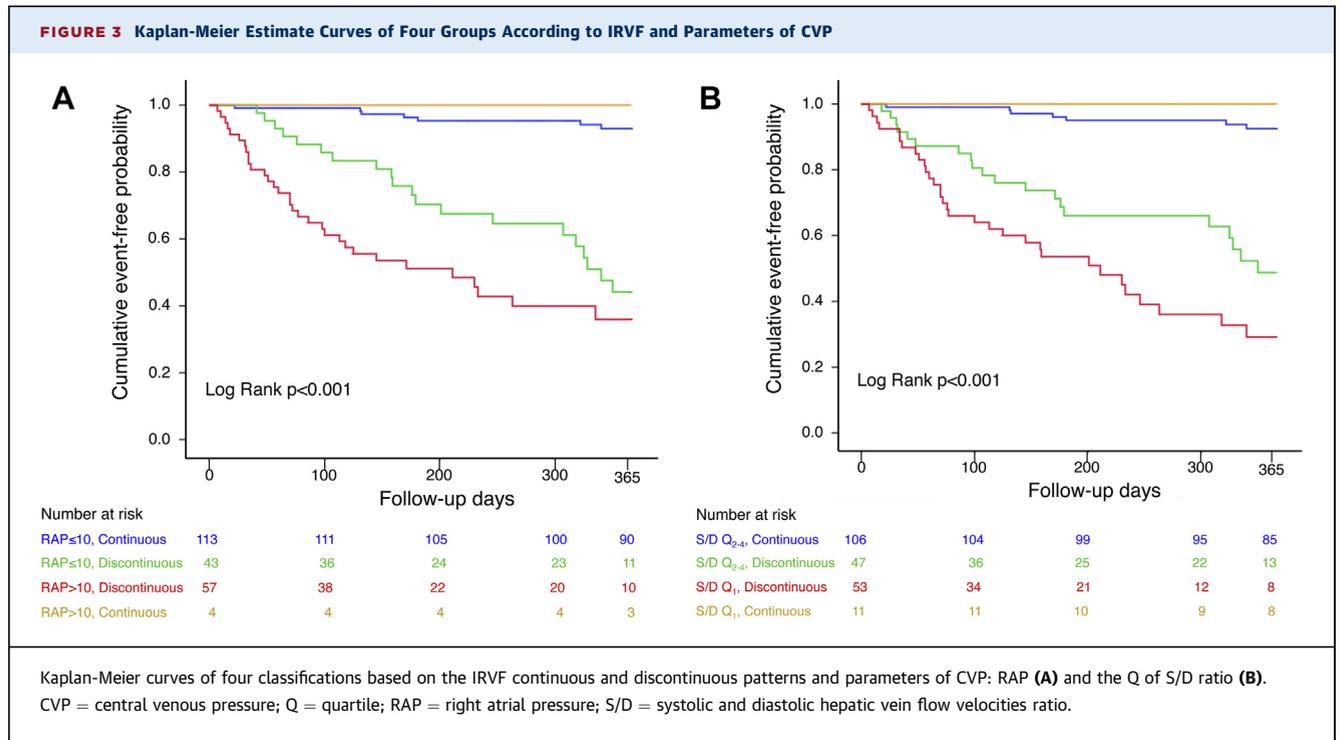
TABLE 2 Multivariate Logistic Regression Analyses for Predictors of IRD Profiles

RI ≥ 0.70		OR (95% CI)	p Value
Model 1	Age (per 1-yr increase)	1.03 (1.01-1.05)	0.01
	Hemoglobin (per 1-g/dl increase)	0.87 (0.76-0.99)	0.04
	Estimated RAP >10 mm Hg	2.88 (1.50-5.55)	0.002
Model 2	Age (per 1-yr increase)	1.04 (1.01-1.07)	0.003
	PCWP (per 1-mm Hg increase)	1.10 (1.03-0.08)	0.005
Biphasic Pattern			
Model 1	BNP (per 100-pg/ml increase)	1.04 (0.96-1.08)	0.08
	Estimated RAP >10 mm Hg	2.23 (1.19-4.52)	0.02
Model 2	Mean RAP (per 1-mm Hg increase)	1.12 (1.01-1.25)	0.03
Monophasic Pattern			
Model 1	RV-FAC (per 10% increase)	0.66 (0.45-0.97)	0.03
	Moderate or severe TR	3.09 (1.04-9.19)	0.04
	Estimated RAP >10 mm Hg	25.8 (8.48-78.5)	<0.001
Model 2	HV-S/D <0.55 (lower quartile)	7.93 (2.9-21.4)	<0.001
	Sodium (per 1-mEq/L increase)	3.43 (1.70-6.94)	0.001
	HV-S/D <0.55 (lower quartile)	12.6 (2.52-63.2)	0.0002
	Mean RAP (per 1-mm Hg increase)	1.33 (1.11-1.61)	<0.001

Model 1 = multivariate model without catheterization data in entire cohort. Model 2 = subanalysis model combined with catheterization data in 103 patients.
 IRD = intrarenal Doppler ultrasound; other abbreviations as in Table 1.

FIGURE 2 Kaplan-Meier Estimate Curves According to IRVF





than in patients with hypertension, and increased RI was independently associated with poor prognosis. Ohuchi et al. (13) focused on RI in hospitalized patients with adult congenital heart disease and a history of biventricular repair. Therefore, the present

study is the first to focus on RI in various types of HF. Along with IRVF, estimated RAP was also related to increased RI. Ohuchi et al. (13) also reported that CVP correlated with RI in addition to mean blood pressure and cardiac index. However, unlike IRVF, RI was not independently associated with clinical outcome. The insignificance association might be related to the indication that primary extrarenal conditions associated with cardiovascular disease may not make RI a specific test of renal disease (22,23). Atherosclerosis and nephropathy caused by coexistent hypertension and diabetes primarily increase intrarenal arterial resistance and reduce compliance. Therefore, the various factors associated with cardiovascular disease may make RI less specific in assessing renal congestion in HF compared to the IRVF profile.

IRVF AND PROGNOSIS. We showed that the IRVF pattern was strongly associated with clinical outcome in patients with HF. This finding may be supported by the effect of renal congestion on prognosis of HF (4,5). Echocardiographic measurements of inferior vena cava and HV flow have been used to estimate RAP in the clinical setting (20). However, compared to the RAP grades, IRVF patterns could distinguish the clinical outcomes. In addition, IRVF was significantly better at predicting clinical outcomes than HV-S/D classifications, although the HV flow pattern might have similar determinants including CVP and TR. The superiority of IRVF may be related to the following

TABLE 3 Predictors of Death From Cardiac Causes or Unplanned Hospitalization for Heart Failure by the Cox Proportional Hazard Model

Predictor	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
NYHA functional class III or IV	4.13 (2.34-7.26)	<0.001		
Hemoglobin (per 1 g/dl increase)	0.79 (0.70-0.88)	<0.001		
BUN (per 10 mg/dl increase)	1.31 (1.14-1.50)	<0.001		
eGFR (per 10 ml/min/1.73 m ² increase)	0.98 (0.97-0.95)	0.006		
Sodium (per 1 mEq/l increase)	0.84 (0.74-0.91)	<0.001	0.93 (0.86-0.99)	0.02
BNP (per 100 pg/ml increase)	1.06 (1.04-1.08)	<0.001	1.05 (1.02-1.07)	<0.001
Use of loop diuretics	2.39 (1.38-4.16)	0.002		
LVEF (per 10% increase)	0.85 (0.76-0.94)	0.002		
E/E' >15	2.77 (1.66-4.64)	<0.001		
LAVI (per 10-ml increase)	1.19 (1.09-1.30)	<0.001		
RV-FAC (per 10% increase)	0.67 (0.55-0.79)	<0.001		
Moderate or severe TR	2.81 (1.60-4.93)	<0.001		
RAP >10 mm Hg	5.26 (2.93-9.43)	<0.001		
RI \geq 0.70	1.78 (1.06-3.00)	0.03		
HV-S/D <0.55 (lower quartile)	3.99 (2.38-6.69)	<0.001		
IRVF biphasic pattern	8.23 (3.45-19.7)	<0.001	6.85 (2.82-16.6)	<0.001
IRVF monophasic pattern	23.1 (10.0-53.5)	<0.001	17.8 (7.62-41.9)	<0.001

Abbreviations as in Tables 1 and 2.

findings: the biphasic pattern showed a poorer prognosis than the continuous pattern, despite the modest relation between the biphasic pattern and CVP. In addition, as shown in **Figure 3**, discontinuous IRVF showed a poorer prognosis than that in the continuous pattern, even in the lower CVP stratum. It is important, of course, that increased CVP relates to discontinuous IRVF as mentioned above, but this most certainly is not the only problem, and it suggests that other factors related to the exacerbation of HF also affect IRVF (23-27). There is longstanding evidence that renal venous congestion influences the sympathetic nervous system and renin-angiotensin-aldosterone systems (28). Effective circulatory volume is determined not only by the volume but also by venous tone controlled by the sympathetic nervous system (25). In particular, splanchnic veins are more sensitive to stimulation by the sympathetic nervous system than are non-splanchnic venous vessels. In the kidney, activation of the sympathetic nervous system causes renal vasoconstriction and worsening of the GFR (26,27). In addition to the traditional effects of renal venous hypertension on intra- and extrarenal hemodynamics and neurohormonal pathways, there has been growing interest in inflammatory and endothelial cell activation (29). The diverse mechanisms lead to a reduction in intrarenal venous compliance, which may be visualized as the discontinuous IRVF pattern, even in patients with normal or mildly elevated CVP. Thus, based on the strong relationship between IRVF and clinical outcomes and on the possibility of multilateral relationships with the exacerbating factor of HF, IRVF may be a useful visual biomarker to stratify vulnerable HF patients.

IRD AND WRF. Worsening renal function was not a significant factor associated with events. In addition, the prevalence of WRF did not differ significantly between the IRVF patterns. In particular, WRF occurred even in 18 patients with continuous flow and without events, which may mean that aggressive decongestion was associated with improved clinical outcomes despite WRF during therapy for acute HF (30-32). In contrast, the prevalence of WRF in the monophasic pattern was increased, but not significantly so, compared to the continuous and biphasic patterns. With decreased eGFR level under stable conditions in the monophasic pattern, renal dysfunction is an important pathophysiological correlate of poor prognosis in HF; however, Worsening renal function would be associated with intrinsic renal function in addition to decongestion.

STUDY LIMITATIONS. As shown in **Table 2**, the determinants of IRD profiles were assessed in 2 models

because catheterization studies were not performed in all subjects. The RAP was common as the determinant of IRVF, but some variables were different between the models. Therefore, this study might not conclude the determinants of IRD profiles other than RAP. In future, large-scale comprehensive clinical studies and basic experimental validation studies are needed to identify the determinants of IRD profiles.

In addition, as shown in **Table 3**, the 95% CI of the hazard ratio for the IRVF in the multivariate Cox proportional hazard model was wide, which meant a low event rate in our study. Therefore, the ability of IRD to predict clinical outcomes in HF must be assessed in a large-scale, multicenter study. In addition, the present study could not determine how concomitant factors including diabetes, hypertension, nephropathy, neurohormonal factors, endothelial function, and inflammation contribute to IRD profiles through the changes of intrarenal vessel function and parenchymal conditions. Therefore, future studies are needed to clarify the related pathophysiology.

CONCLUSIONS

IRVF patterns, rather than arterial RI, were associated with RAP levels. More importantly, the IRVF pattern correlated strongly with clinical outcomes independent of conventional prognostic factors of HF including RAP levels. Therefore, the IRVF pattern may be a useful visual biomarker of renal congestion, providing additional information to stratify vulnerable HF patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Yoshihiro Seo, Cardiovascular Division, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba 305-8575, Japan. E-mail: yo-seo@md.tsukuba.ac.jp.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Intrarenal Doppler ultrasonography is a useful method for assessing intrarenal hemodynamics in patients with heart failure. In particular, intrarenal venous flow may be associated with exacerbating factors of HF including renal congestion.

TRANSLATIONAL OUTLOOK: The pathophysiological determinants of IRD profiles should be investigated through clinical and basic research to make IRD a guide for HF therapy.

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KEY WORDS cardiorenal syndrome, Doppler ultrasound, heart failure, prognosis, renal congestion

APPENDIX For supplemental tables, please see the online version of this article.