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ORIGINAL ARTICLE
Imaging

Doppler-Derived Intrarenal Venous Flow Mirrors Right-Sided Heart Hemodynamics in Patients With Cardiovascular Disease

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Background: Interruption in Doppler intrarenal venous flow (IRVF) has been used in assessing renal congestion and in the prediction of prognosis of cardiovascular diseases. However, there is a paucity of pathophysiological knowledge, so we aimed to clarify the determinants of IRVF interruption.

Methods and Results: Intrarenal Doppler studies were performed within 24 h before right-side catheterization studies. The interruption in IRVF in 73 patients was divided into a continuous pattern, and 4 discontinuous types based on the timing of interruption. Type 1, with an interruption in early systole, was associated with a-wave elevation of right atrial pressure (RAP). Type 2, with an interruption in early diastole, was associated with v-wave elevation, tricuspid regurgitation (TR), and right ventricular dysfunction. Both Type 1 and 2 were observed even in the normal range of mean RAP. Type 3, with an interruption throughout systole, was observed in advanced right heart failure patients with markedly elevated RAP, particularly elevated x-descend and atrial fibrillation. Finally, Type 4, with limited flow at systole, was observed in 2 of the patients with pulmonary arterial hypertension.

Conclusions: IRVF interruption was closely related to RAP elevation at each specific point of the cardiac cycle rather than to mean RAP levels, suggesting that the characteristics of IRVF mirror right-sided heart hemodynamics, not mean RAP.

Key Words: Hemodynamics; Renal Doppler ultrasound; Right-side heart

Amid growing attention to renal congestion in heart failure (HF), evidence is accumulating for Doppler-derived intrarenal venous flow (IRVF) being a reliable and feasible visual biomarker in not only renal circulation assessments but also as a predictor of prognosis in cardiovascular diseases.[1–8] Thus, assessment of IRVF might help guide decongestive therapy, but more detailed information is needed.[9]

Changes in IRVF, pulsatility and interruption, are mainly determined by central venous pressure (CVP).[3] However, even when CVP remains within the normal range or slightly increased, some types of IRVF interruption are observed and associated with worsened clinical outcomes compared with a continuous flow pattern. A previous sophisticated study[4] reported that increased pulsatility or interruption of IRVF was observed a few milliseconds after the P- and T-waves. The researchers hypothesized that small increases during right atrial (RA) and right ventricular (RV) contraction can induce larger pressure waves in the inferior vena cava and intermittently interrupt forward flow in the interlobar veins in the setting of decreased venous compliance. Recently, we reported supporting data that increased pulsatility of the IRVF is associated with renal interstitial pressure elevation caused by not only renal congestion but also interstitial fibrosis in a Dahl rat hypertensive HF model.[10] Thus, previous studies have revealed pathophysiological aspects of IRVF step by step, pathophysiological knowledge is still scarce. Then, we aimed to clarify the determinants of IRVF interruptions in patients with cardiovascular diseases.

Methods

Study Design

Patients who underwent right heart catheterization studies and intrarenal Doppler (IRD) studies, and comprehensive echocardiographic examinations between February 2015 and August 2019 at the University of Tsukuba Hospital were retrospectively enrolled. Of them, patients who underwent the IRD study within 24 h before catheterization were eligible. Patients with inadequate IRD images were excluded. The investigation conformed with the principles outlined in the Declaration of Helsinki and the institutional ethical committee approved the protocol. Patients were given online information about opting (http://www.md.tsukuba.ac.jp/clinical-med/cardiology/research_group/

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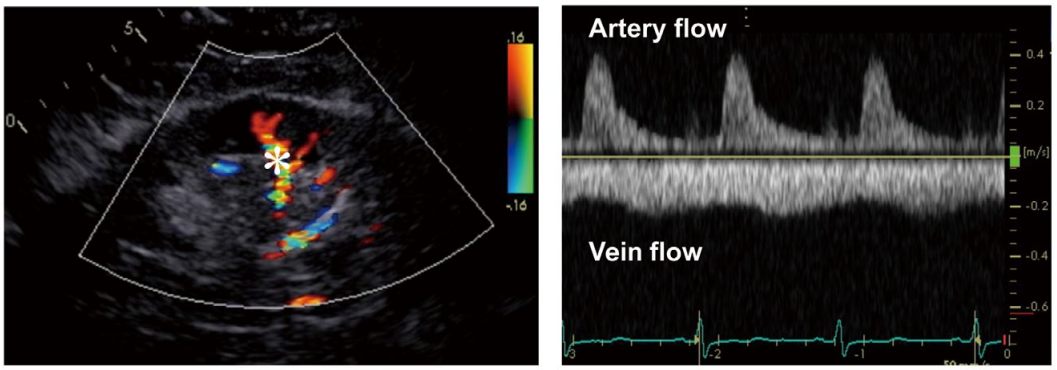

Figure 1. (**Left panel**) Color Doppler flow image from the right kidney. *Doppler sample volume position in the interlobar vessels. (**Right panel**) Intrarenal arterial and venous flow.

Table 1. Comparisons of Patients' Clinical Characteristics According to the IRVF Pattern

	Total (n=73)	Continuous (n=29)	Type 1 (n=23)	Type 2 (n=7)	Type 3 (n=13)	Type 4 (n=2)	P value
Age, years	56±18	60±16	46±19*,#	51±17	65±16	30 s, 40 s	0.006
Men	37 (52)	16 (55)	10 (46)	70 (29)	24 (69)	Case 1	0.32
SBP, mmHg	115±21	112±20	124±23	115±14	108±17	93, 90	0.12
DBP, mmHg	65±13	64±12	69±15	64±14	66±11	58, 54	0.58
Mean BP, mmHg	83±15	80±14	88±17	79±11	82±13	58, 60	0.33
Heart rate, beats/min	74±15	74±12	74±13	73±12	74±12	80, 78	0.73
AF	13 (18)	4 (14)	0	1 (7.7)	7 (54)	–	0.003
Hypertension	25 (35)	11 (38)	6 (27)	0	8 (61)	–	0.04
Diabetes	16 (23)	7 (24)	3 (14)	2 (29)	4 (31)	–	0.63
NYHA class III or IV	29 (41)	13 (45)	5 (17)	2 (6.9)	9 (31)	Both cases	0.047
Laboratory data							
Hemoglobin, g/dL	13±2.5	13±2.2	13±2.9	12±2.3	11±2.1	11, 12	0.06
BUN, mg/dL	19±9.1	18±5.1	15±4.7	16±3.6	29±16†	9, 17	<0.001
eGFR, mL/min/1.73 m^2	75±24	80±24	77±20	68±19*	46±14†	83, 76	<0.001
Sodium, mEq/L	140±3.3	139±3.0	141±2.4	140±2.3	138±5.0	139, 140	0.05
logBNP, pg/mL	2.1±0.7	2.1±0.6	1.9±0.7	2.2±0.4	2.6±0.3*,‡	1.5, 2.3	0.009

Values are mean±SD or number (%). In Type 4, Case 1 data are shown on the left and Case 2 data on the right. *P<0.05 vs. continuous pattern, #P<0.05 vs. Type 3, †P<0.05 vs. other types, ‡P<0.05 vs. Type 2. AF, atrial fibrillation; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; IRVF, intrarenal venous flow.

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Ultrasound Study

The IRD studies were performed with a Vivid E95 system (GE Healthcare, Horton, Norway) as previously reported (**Figure 1**)[3] The IRVF patterns were jointly determined by N.I. and Y.S. The discontinuous flow types had >1 phases with zero velocity. Comprehensive echocardiographic studies of both the left and right sides of the heart were performed according to established guidelines.[11,12] Left ventricular ejection fraction (LVEF) was measured using the biplane disk summation method. The ratio of early diastolic mitral inflow velocity (E) to the average peak early mitral annular velocities of the septal and lateral wall corner (e′) was calculated as E/e′. The degree of tricuspid regurgitation (TR) was assessed by the vena contracta width of the TR jet. TR severity, the fractional area change of the right ventricle (FAC), and the RAP grade were assessed as per the guideline.[12]

Cardiac Catheterization

Right heart catheterization was performed with a 7Fr balloon-tipped pulmonary artery catheter (Swan-Ganz, Baxter Healthcare, Irvine, CA, USA). The RAP curve was analyzed at the a-wave, c-wave, x-descent, v-wave, and the y-descent.[13] In cases of atrial fibrillation (AF), the c-wave was used instead of the a-wave.

Statistical Analysis

One-way analysis of variance (ANOVA) with the post-hoc Tukey-Kramer test was used to compare variables between IRVF patterns. Comparisons between groups were performed using the χ^2 test for categorical variables. The power to predict each interruption point of the IRVF was assessed using the area under the receiver-operating characteristic (ROC) curve. Independent determinants of each

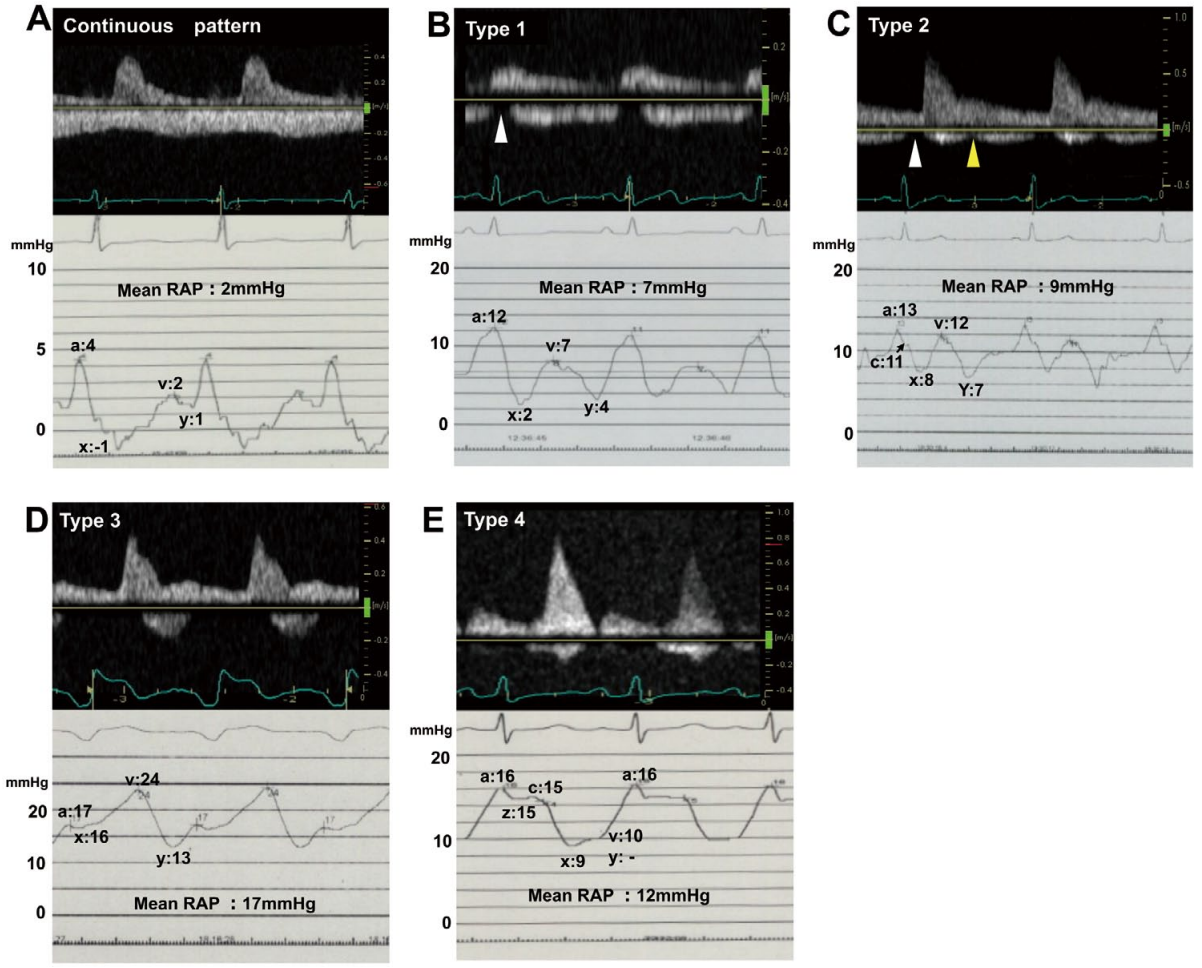

Figure 2. (**A**–**E**) Intrarenal venous flow (IRVF) and right atrial pressure (RAP) curve in each representative case of the patterns of venous blood flow. (**B**,**C**) White arrowhead shows the systolic interruption point. (**C**) Yellow arrowhead shows the diastolic interruption point. Details are explained in the text.

IRVF interruption point were assessed by multivariable logistic regression analyses using univariate factors with a value of $P<0.05$. Because Type 4 consisted of only 2 unique subjects with PAH, they were excluded from the statistical analysis.

Statistical analyses were performed with SPSS ver. 25 (SPSS Inc., Chicago, IL, USA) and the box plot analyses were performed with R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We excluded 6 patients because of inadequate IRVF images, so 73 patients were analyzed. Their clinical characteristics are summarized in **Table 1**. We studied various heart diseases, including left-sided heart diseases, pulmonary arterial hypertension (PAH), congenital heart diseases, and valvular diseases (summarized in the **Supplementary Table**).

IRVF Pattern

IRVF was classified into a continuous flow pattern and 4 discontinuous flow types (**Figure 2**). Type 1 was defined as IRVF with a systolic interruption point. Type 2 was IRVF with 2 interruption points in both the systolic and diastolic phase. In type 3, IRVF interruption was limited at the early diastolic phase. Type 4 was observed in 2 patients with PAH, in which limited flow was observed in the systolic phase, but not during the diastolic phase. The clinical characteristics of the IRVF types are summarized in **Table 1**, from which Type 4 is excluded because it comprised only 2 patients.

The Type 1 group was significantly younger than the continuous and Type 3 groups. The prevalence of AF was higher in the Type 3 group in than other groups. The estimated glomerular filtration rate (eGFR) in the Type 2 group was lower than in the continuous group. In the Type 3 group, the plasma B-type natriuretic peptide (BNP) level was higher than in the continuous and Type 1 groups.

The comparison of the ultrasound and catheterization data is summarized in **Table 2**. LVEF did not differ between groups. E/E' was significantly higher in the Type 3 group compared with the continuous and Type 1 groups. RV-FAC in the Type 3 group was significantly lower than

Table 2. Comparison of Ultrasound and Catheterization Data According to the IRVF Pattern

	Total (n=73)	Continuous (n=29)	Type 1 (n=23)	Type 2 (n=7)	Type 3 (n=13)	Type 4 (n=2)	P value
Echocardiographic data							
LVEF, %	54±19	54±19	58±19	60±7.4	44±20	71, 54	0.13
E/E'	12±7.6	11±6.4	9.7±4.7	14±11	20±8.6*,#	6.6, 9.5	0.001
RV-FAC, %	36±11	40±11	38±11	31±12	29±7.5*	24, 7.1	0.02
Moderate/severe TR, (%)	22/9 (31/13)	5/1 (17/3)	7/1 (32/5)	5/1 (71/14)	5/6 (39/46)	Case 1	<0.001
RAP grade 3/8/15 mmHg	47/10/14	27/2/0	16/5/1	4/2/1	0/1/12	8, 15	<0.001
Catheterization data							
PCWP, mmHg	14±7.0	11±3.2	13±6.6	15±8.9	22±6.5*,#	6, 10	<0.001
Mean PAP, mmHg	28±15	20±7.5	33±23*	30±11	31±7.8*	51, 68	0.01
RVEDP, mmHg	10±5.5	6.5±3.5	11±3.6*	13±4.3*	16±5.3†	11, 26	<0.001
Mean RAP, mmHg	7.8±5.3	4.1±2.1	7.6±2.2*	8.6±3.8*	16±6.0†	6, 12	<0.001
a wave, mmHg (n=number)	9.8±4.4 (n=58)	6.2±2.5 (n=25)	11±2.2 (n=21)*	12±4.9 (n=6)*	17±3.6 (n=6)*,#	10, 17	<0.001
c wave in AF, mmHg	13±7.5 (n=13)	5.0±0.8 (n=4)	11 (n=1)	12 (n=1)	18±6.5 (n=7)	–	–
x descent, mmHg	5.9±5.1	2.5±2.1	4.9±2.3*	7.4±3.2*	14±4.3†	0, 11	<0.001
v wave, mmHg	9.6±7.2	4.8±2.1	8.5±2.2*	12±2.9*	21±9.3†	4, 12	<0.001
y descent, mmHg	6.3±4.4	3.8±2.1	6.3±3.1	7.0±3.6	11±6.1*,#	4, 10	<0.001
CI, L/min/m^2	3.0±1.1	3.0±0.7	3.4±1.3	2.9±1.1	2.7±1.1	2.6, 2.1	0.36

Values are mean±SD or number (%). *P<0.05 vs. continuous pattern, #P<0.05 vs. Type 2, †P<0.05 vs. other types. CI, cardiac index; E/E', ratio of early diastolic peak velocity of Doppler transmitral flow to early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure, RV-FAC, right ventricular fractional area change ratio; SBP, systolic blood pressure; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

in the continuous group. The prevalence of significant TR was higher in the Type 2 and 3 groups. Pulmonary capillary wedge pressure (PCWP) in the Type 3 group was higher than in the continuous and Type 1 groups. Mean pulmonary arterial pressure (PAP) in the Type 1 and 3 groups was higher than in the continuous group. RV end-diastolic pressure (RVEDP) in the Type 1–3 groups was significantly higher than in the continuous group. In particular, the Type 3 group had higher RVEDP compared with the other groups. Mean RAP in the Type 1–3 groups was higher than in the continuous group, and that in the Type 3 group was significantly higher than in the other groups. In the comparisons of the a-wave in sinus rhythm patients, the Type 1–3 groups had a higher a-wave than the continuous group, and that in the Type 3 group was significantly higher than in the Type 1 group (**Figure 3**). In AF patients, the c-wave showed a similar tendency to that of the a-wave in sinus rhythm patients. In the comparisons of the x-descent and v-wave, the Type 3 group had the highest values compared with other groups. Also, those values in the Type 2 and 3 groups were significantly higher than in the Type 1 group. The y-descend showed a higher value in the Type 3 group than in the continuous and Type 1 groups.

Interaction Between IRVF and RAP

As shown in **Figure 2**, a representative case in the continuous group, a patient with a prior myocardial infarction had continuous IRVF with mild pulsatility. In the Type 1 case of a patient with dilated cardiomyopathy, a short interruption is observed in the early to mid-systolic phase, the timing of which corresponds to the a-wave of 12 mmHg. Meanwhile, the v-wave is 7 mmHg, showing continuous diastolic flow at that point. In the Type 2 case of a previously repaired atrial septal defect and severe TR, the IRVF shows 2 short interruptions, 1 in early to mid-systolic phase, which corresponds to the a-wave of 13 mmHg and the c-wave of 11 mmHg, and the other in the early diastolic phase, corresponding to the v-wave of 12 mmHg. In the Type 3 case of a patient with dilated cardiomyopathy, mean RAP is elevated at 17 mmHg. From the a-wave to the v-wave through the x-descend, the RAP trace is >16 mmHg, during which the IRVF is continuously interrupted. IRVF is observed in the early diastolic phase only, with the timing corresponding to the y-descend of 13 mmHg. Finally, a Type 4 case of a patient with severe PAH (case 2 in **Tables 1** and **2**) shows the unique monophasic pattern of IRVF. There is a long duration from the p-wave on ECG to the onset of renal artery flow, so a shallow z-descend between the a-wave and c-wave is observed. Because IRVF is present in the same phase of renal artery flow, it is thought that the timing of the flow corresponds to the x-descent. Due to delayed RV relaxation and the short duration of the diastolic phase, the y-descend cannot be detected. Therefore, early diastolic flow was not apparent in the Type 4 cases.

The common feature among types 1–3 is an interruption of IRVF in the early systolic phase. As shown in **Figure 3**, the a-wave, the c-wave in AF, the x-descent, and the v-wave in the Type 1–3 groups were significantly higher than in the continuous group. The ROC curve analyses for interrupted IRVF in the early systolic phase, which was for the continuity of IRVF also, revealed the highest AUC in the a-wave (AUC 0.962, P<0.001), followed by the v-wave (AUC 0.927, P<0.001) (**Table 3**). The important point is that the sensitivity of the normal range of mean RAP (≤8 mmHg) for continuity of IRVF was only 0.6.

Secondly, the common feature of types 2 and 3 is an interruption of IRVF in the early diastolic phase. The ROC curve analysis for the interruption of IRVF in the

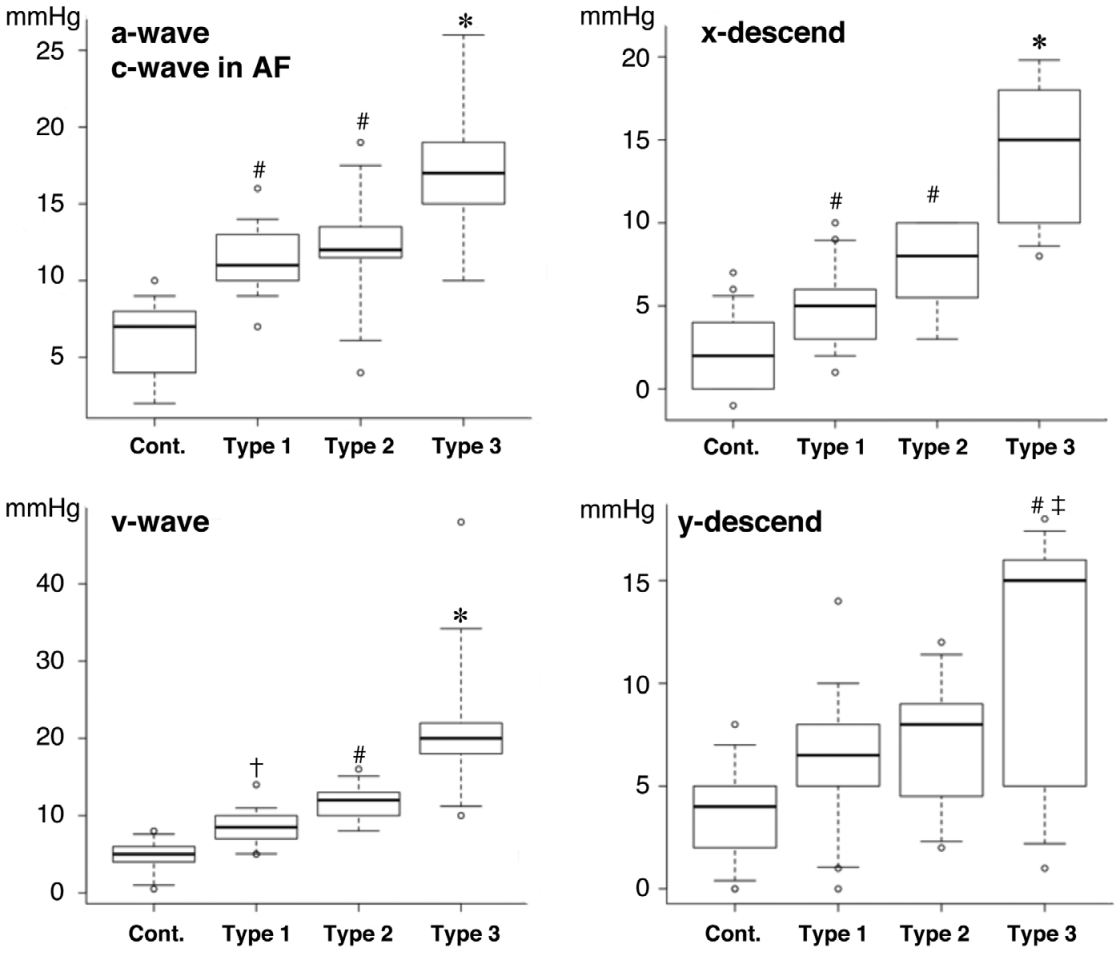

Figure 3. Comparisons of each point in the right atrial pressure curve between the types of intrarenal venous flow. *P<0.001 vs. other types, #P<0.001 vs. Cont., †P<0.01 vs. Cont., ‡P<0.01 vs. Type 1. AF, atrial fibrillation; Cont., continuous pattern.

early diastolic phase revealed the highest AUC in the v-wave (AUC 0.926, P<0.001), followed by the x-wave (AUC 0.895, P<0.001). Mean RAP ≥9 mmHg also showed AUC of 0.861, and mean RAP ≥9 mmHg had a relatively high accuracy for detection of an interruption of IRVF in the early diastolic phase.

Finally, the feature of Type 3 is IRVF that is limited to the early to mid-diastolic phase, which means the feature is continuous interruption of IRVF through the systolic phase. The ROC curve analysis for the continuous interruption of IRVF through the systolic phase revealed the highest AUC in the x-wave (AUC 0.974, P<0.001), followed by the v-wave (AUC 0.972, P<0.001). Mean RAP had an AUC of 0.928, and mean RAP ≥9 mmHg had relatively high accuracy for detection of continuous interruption of IRVF through the systolic phase.

Determinants of IRVF

The results of logistic regression analyses to identify the determinants of each IRVF interruption are summarized in **Table 4**. For interruption in the early systolic phase, 5 factors, comprising mean PAP, PCWP, mean RAP ≥6 mmHg, a-wave ≥10 mmHg, and more than moderate level of TR, were significantly associated in the univariate analyses. Because mean RAP and the a-wave had a strong correlation (R=0.91), multivariable logistic regression analyses were performed separately. Mean RAP ≥6 mmHg and a-wave ≥10 mmHg were identified as the single independent determinant of interruption in the early systolic phase in each regression model.

For the interruption in the early diastolic phase, 7 factors, comprising AF, eGFR, logBNP, mean RAP ≥9 mmHg, v-wave ≥12 mmHg, FAC, and significant TR, were significantly associated in the univariate analyses. Because early diastolic interruption was observed in only 20 patients and there was a strong correlation between mean RAP and the v-wave (R=0.92), multivariable logistic regression analyses were performed separately using a combination of the 2 factors, namely mean RAP ≥9 mmHg or v-wave ≥12 mmHg, and each of the other factors. As a result, FAC or significant TR in each regression model was associated with interruption in early diastolic phase independent of mean RAP ≥9 mmHg or v-wave ≥12 mmHg.

Finally, for continuous interruption through the systolic phase, the most parameters were significantly associated in the univariate analyses. Because interruption through the

Table 3. ROC Curve Analysis for Continuous and Interrupted Types of IRVF

Type of IRVF	AUC	P value	95% CI	Cutoff value, mmHg	Sensitivity	Specificity	Accuracy
1. Continuous							
Mean RAP	0.906	<0.001	0.84–0.97	≤5	0.76	0.88	0.92
				≤8	0.60	1.0	0.73
a-wave	0.962	<0.001	0.92–1.00	≤9	0.97	0.89	0.92
2. Interruption in the early systolic phase							
Mean RAP	0.906	<0.001	0.84–0.97	6	0.86	0.75	0.82
a-wave	0.962	<0.001	0.92–1.00	10	0.89	0.97	0.92
3. Interruption in the early diastolic phase							
Mean RAP	0.861	<0.001	0.76–0.96	9	0.77	0.84	0.82
v-wave	0.926	<0.001	0.85–1.00	12	0.82	0.98	0.92
4. Interruption throughout the systolic phase							
Mean RAP	0.928	<0.001	0.84–1.00	9	0.92	0.78	0.80
x-wave	0.974	<0.001	0.94–1.00	9	0.92	0.90	0.90

AUC, area under the curve; ROC, receiver-operating characteristic. Other abbreviations as in Tables 1,2.

Table 4. Determinants of IRVF Interruption

Type of IRVF	Univariate analysis			Multivariable analysis					
				Model 1			Model 2		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
1. Interruption in early systolic phase									
Mean PAP, per 1 mmHg increase	1.11	1.04–1.18	0.001	1.08	1.003–1.16	0.04			0.48
PCWP, per 1 mmHg increase	1.14	1.04–1.25	0.006			0.88			0.90
Mean RAP ≥6 mmHg	24.5	6.95–86.5	<0.001	20.4	3.5–117	0.001	–	–	–
a-wave ≥10 mmHg	218	24.2–1,973	<0.001	–	–	–	124	8.8–1,741	<0.001
TR ≥ moderate	6.09	2.06–18.0	0.001			0.11			0.62
2. Interruption in the early diastolic phase									
AF	6.71	1.76–25.6	0.005						
eGFR, per 1 mL/min/1.73 m^2 increase	0.97	0.95–0.99	0.02						
logBNP, per 1 increase	3.42	1.34–8.65	0.009						
Mean RAP ≥9 mmHg	18.3	5.23–63.8	<0.001	21.4	4.96–92.4	<0.001	17.6	3.91–78.9	<0.001
v-wave ≥12 mmHg	225	23.6–2,148	<0.001	236	20.4–2,723	<0.001	191	14.6–2,509	<0.001
FAC ≤36%	7.44	2.33–23.7	0.001						
Mean RAP				9.11	2.05–40.5	0.004			
v-wave				9.49	1.002–90.7	0.047			
TR ≥ moderate	7.67	2.89–20.5	<0.001						
Mean RAP							16.1	3.18–81.1	0.001
v-wave							13.3	1.34–133	0.02
3. Interruption throughout the systolic phase									
AF	12.8	3.09–53.2	<0.001	12.2	1.07–139	0.04			
eGFR, per 1 mL/min/1.73 m^2 increase	0.92	0.88–0.96	0.001						
Hb, per 1 g/dL increase	0.71	0.53–0.95	0.02						
logBNP, per 1 increase	6.69	1.81–24.8	0.004				11.3	1.18–108	0.03
PCWP, per 1 mmHg increase	1.25	1.11–1.41	<0.001						
Mean RAP ≥9 mmHg	43.4	5.15–365	<0.001						
x-wave ≥9 mmHg	108	11.9–982	<0.001	105	9.08–1,217	<0.001	121	9.55–1,539	<0.001
FAC ≤36%	9.50	1.92–46.8	0.006						
TR ≥ moderate	3.446	1.53–7.71	0.003						

OR, odds ratio, Other abbreviations as in Tables 1–3.

systolic phase was observed only in 13 cases, multivariable logistic regression analyses were performed for reference using the same method as for interruption in the early diastolic phase. In the regression model using mean RAP ≥9 mmHg, each factor was significantly associated with the interruption. In contrast, in the regression model using x-wave ≥9 mmHg, only AF and logBNP were independently associated with the interruption.

Discussion

This study demonstrated the IRVF can be classified into a continuous pattern and 4 discontinuous types based on the timing of the IRVF interruption. The interruptions were strongly affected by elevation of each specific RAP point during the cardiac cycle rather than by the mean RAP level. As well, the presence of a specific threshold of the RAP point was clarified for each IRVF interruption. In Type 1, with an interruption of IRVF in the early systolic phase, which was associated with an elevated a-wave, the interruption occurred even in patients within the normal range of mean RAP. Type 2 with an interruption of IRVF in the early diastolic phase was associated with significant TR and RV dysfunction accompanied by an elevated v-wave. Type 3 with continuous interruption of IRVF through the systolic phase was observed in more advanced right HF patients with markedly elevated RAP, in particular an elevated x-descend. Also, AF contributed to Type 3 IRVF. Finally, Type 4 with limited flow at the systolic phase was observed in the 2 patients with PAH.

RAP Wave and IRVF Pattern

Classically, the jugular venous pressure has been analyzed as a surrogate of mean RAP and the hemodynamic effects in the right atrium. Namely, the RA filling and contraction and RV filling dynamics cause changes in venous flow and pressure, which produces pulsations in the central veins that are transmitted toward the peripheral veins, opposite to the direction of blood flow.[12] In the clinical setting, Doppler ultrasound evaluation of hepatic vein flow reflects the hemodynamics of the RA.[14] A normal wave in the hepatic vein has 3 components, including retrograde A wave, an antegrade S wave, a transitional V wave (which may be antegrade, retrograde, or neutral), and an antegrade D wave. In central venous pulsation, as shown in both the normal jugular pulse and hepatic vein flow, the a-wave has retrograde characteristic. In contrast, IRVF in normal subjects has monophasic or continuous flow with a little pulsation, which is rather an abnormal pattern in the hepatic vein.[15] Because the intrarenal vein is located far from the RA, IRVF may be less sensitive to a change of RAP within the normal range.

A feature of Type 1 IRVF was the association with an elevated a-wave, which transmits to the intrarenal vein and the IRVF interruption occurs in early systole. Interestingly, the interruption may occur even in the normal range of RAP. In our series, Type 1 was mainly observed in PAH and congenital heart diseases (**Supplementary Table**). The finding suggests that a RV filling abnormality as shown by elevated RVEDP compared with a continuous pattern may be the primary pathophysiology of Type 1. Only in 1 case of AF did the patient show Type 1 IRVF, which was caused by an elevated c-wave produced by a bulging of the tricuspid valve into the RA during the RV isovolumic systolic phase. Thus, even in the normal range of mean RAP, the intrarenal venous circulation may reflect a subclinical RV filling abnormality and suggests a risk of renal congestion with greater volume overload.

Type 2 IRVF, of which there were relatively few cases, showed an early diastolic IRVF interruption in addition to an early systolic interruption. The key determinant is the elevated v-wave, which is well known to be caused by TR. In fact, significant TR was an independent determinant of Type 2 in this study. In addition, because FAC was also associated with Type 2 IRVF, v-wave elevation was significant because of the elevated RV filling pressure due to advanced RV diastolic dysfunction. As well as with Type 1, approximately one-quarter of the patients with Type 2 showed normal mean RAP even when at high risk of right-sided congestion.

Type 3 IRVF was observed in patients with advanced right-sided congestion. The key determinant was the elevated x-descend, which suggests 2 factors. First, AF was associated with Type 3 IRVF. In AF, loss of atrial contraction reduces atrial relaxation, which in turn decreases the x-descend. Secondly, RA systolic dysfunction due to afterload mismatch against higher RVEDP may be a cause of the x-descend that does not drop. In addition, almost half of the patients had severe TR, which elevates the x-descend with marked elevation of the v-wave. Therefore, due to a continuously elevated RAP from the tricuspid valve closing (higher c-wave) to end-systole (higher v-wave) through systole (higher x-descend), IRVF was interrupted in Type 3. The remaining early diastolic flow may be caused by an increased RAP (higher v-wave) against a higher RV diastolic pressure, which means the RV restrictive filling property. Although cardiac tamponade was not included in our series, it is well known that similar hemodynamics are observed in cardiac tamponade.

Type 4 IRVF was a specific restrictive filling pattern in some of the PAH patients. Loss of the y-descend was the key determinant, suggesting loss of early filling due to shortened RV filling time with RV diastolic dysfunction. Case 2 with severe PAH is compatible with this hypothesis. In contrast, in case 1, RAP and RVEDP were normal. Low filling pressure and slower RV relaxation might cause loss of the early filling pressure.

Other Factors in the Renal Circulation

IRVF interruptions with normal mean RAP support the results of Nijst et al.[4] Recently, we reported intrarenal fibrosis associated with IRVF pulsation in a rat hypertension model, which means that stiffness of the renal parenchyma is also reflected in the IRVF.[10] Such changes around intrarenal vessels may impair vessel compliance, because hepatic vein flow is altered by parenchymal fibrosis in patients with liver cirrhosis.[15–17] Although the renal pathology was not investigated, we consider that renal fibrosis likely occurred because of chronic renal hypoperfusion and the acute decompensation of HF in our study population. Therefore, the compliance of intrarenal veins might be reduced and might be sensitive to right-sided hemodynamic changes even in the setting of normal mean RAP.

The effect of left-side factors, including the cardiac index and blood pressures on IRVF was not apparent in this study. Recent studies have reported no significant association between the cardiac index and renal function, so the effect of the cardiac index may be small on IRVF.[2,18] Because the autoregulation of the renal circulation mainly depends on blood pressure, an acute drop in both systolic

and mean blood pressure may cause worsening renal function in patients with HF.[19,20] In this study, there were no significant differences in systolic, diastolic, and mean blood pressures between groups. However, because this study did not have longitudinal data, the associations between changes in blood pressure and changes in renal circulation could not be assessed.

Study Limitations

This study was designed as a single-center, retrospective study, so the number of subjects might be not enough to identify the determinants of the IRVF pattern. Besides, the study subjects had various diseases. By focusing on more specific cardiac diseases, the features of IRVF might be clarified in each disease. In addition, due to the cross-sectional study, the changes in IRVF by hemodynamic changes, including cardiac rhythm, blood pressure, RAP, and TR, were not assessed. Further large-scale studies are needed to conclude these. Finally, because IRD and the right-side catheterization studies were not performed simultaneously, the time difference might have affected the results. However, the patients were in a stable state of HF, so the time difference may have had little effect, within an acceptable range.

Conclusions

This study demonstrated a close relationship of the intrarenal venous circulation with RA hemodynamics and RV filling properties in cardiovascular diseases. Impairments of the intrarenal venous circulation may occur even in the normal range of mean RAP, and advanced impairment may reflect TR and AF. These findings suggest IRVF may be not only a marker of renal congestion but also a mirror of right-sided heart hemodynamics, including concomitant conditions, not reflected in the mean RAP.

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IRB Information

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Supplementary Files

Please find supplementary file(s);
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