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ORIGINAL ARTICLE
Heart Failure

Demonstration of Improved Renal Congestion After Heart Failure Treatment on Renal Perfusion Imaging With Contrast-Enhanced Ultrasonography

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Background: Renal congestion is a critical pathophysiological component of congestive heart failure (CHF).

Methods and Results: To quantify renal congestion, contrast-enhanced ultrasonography (CEUS) was performed at baseline and after treatment in 11 CHF patients and 9 normal subjects. Based on the time-contrast intensity curve, time to peak intensity (TTP), which reflects the perfusion rate of renal parenchyma, and relative contrast intensity (RCI), an index reflecting renal blood volume, were measured. In CHF patients, TTP at baseline was significantly prolonged compared with that in controls (cortex, 10.8±3.5 vs. 4.6±1.2 s, P<0.0001; medulla, 10.6±3.0 vs. 5.1±1.6 s, P<0.0001), and RCI was lower than that in controls (cortex, −16.5±5.2 vs. −8.8±1.5 dB, P<0.0001; medulla, −22.8±5.2 vs. −14.8±2.4 dB, P<0.0001). After CHF treatment, RCI was significantly increased (cortex, −16.5±5.2 to −11.8±4.5 dB, P=0.035; medulla, −22.8±5.2 to −18.7±3.7 dB, P=0.045). TTP in the cortex decreased after treatment (10.8±3.5 to 7.6±3.1 s, P=0.032), but it was unchanged in the medulla (10.6±3.0 to 8.3±3.2 s, P=0.098).

Conclusions: Renal congestion can be observed using CEUS in CHF patients.

Key Words: Contrast; Heart failure; Renal congestion; Renal perfusion; Ultrasonography

Renal impairment is associated with adverse clinical outcome in patients with congestive heart failure (CHF).[1,2] It is known as cardiorenal syndrome and is widely recognized as an important component of the pathophysiology of CHF. In CHF patients, renal dysfunction is due not only to low cardiac output. Renal congestion caused by elevated central venous pressure (CVP) exacerbates renal impairment, independent of renal blood flow regulated by cardiac output.[3–6] Intrarenal hemodynamics, however, are not well understood in the context of renal congestion, and no previous reports have described the imaging results of renal perfusion impairment in CHF patients.

Real-time contrast-enhanced ultrasonography (CEUS) using low mechanical index (MI) microbubble-based contrast agents is a novel imaging technique used to visualize perfusion of the microvascular bed. When injected i.v., microbubble-based agents have several advantages. First, they traverse pulmonary circulation and remain entirely intravascular; and second, they mix uniformly with blood in the circulation and possess the same intravascular rheology as red blood cells.[7] CEUS has been used in several renal pathophysiological studies.[8,9] It has also been clinically applied as a diagnostic tool for various renal diseases, including changes in renal perfusion early in the course of renal allograft nephropathy[10,11] and renal artery stenosis.[12] Furthermore, it has been experimentally applied in induced acute kidney injury models.[13,14] We recently reported that successful visualization of renal perfusion disturbances using CEUS was possible in rat models of acute renal congestion.[15] Based on these results, we hypothesized that human renal congestion could also be evaluated using CEUS.

Therefore, in this study, we quantified renal congestion in CHF patients on renal perfusion imaging using CEUS.

Methods

Study Design

In total, 11 patients (7 men, 4 women; mean age, 81±8 years) who were hospitalized with a diagnosis of CHF using the Framingham Congestive Heart Failure Diagnostic criteria were enrolled.[16] Obvious symptoms of right-sided HF were recognized in all patients, included leg edema, shortness of breath, pleural effusion, pulmonary hypertension, moderate or severe tricuspid regurgitation (TR), and a decline of inspiratory collapse in the inferior vena cava (IVC). As part of the inclusion criteria for this study, all patients were

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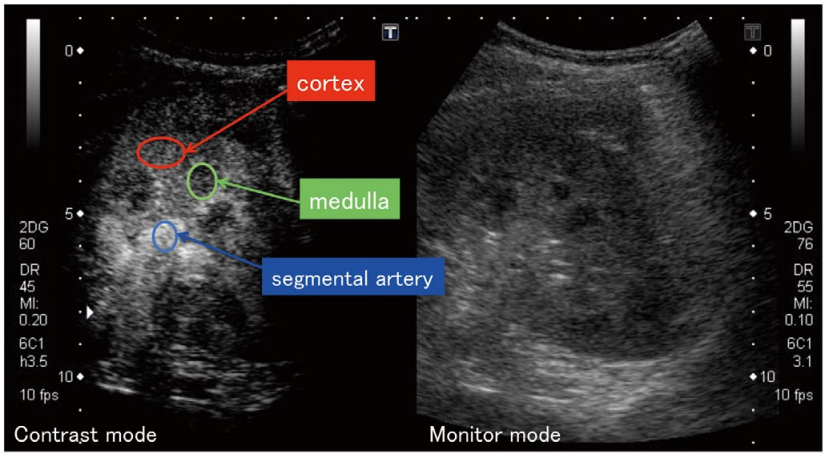

Figure 1. Renal contrast-enhanced ultrasonography of a representative control. (**Left**) Contrast mode and (**Right**) monitor mode. Oval regions of interest were drawn over the middle superficial peripheral renal cortex, medulla, and segmental artery. Average contrast intensity was measured in decibels.

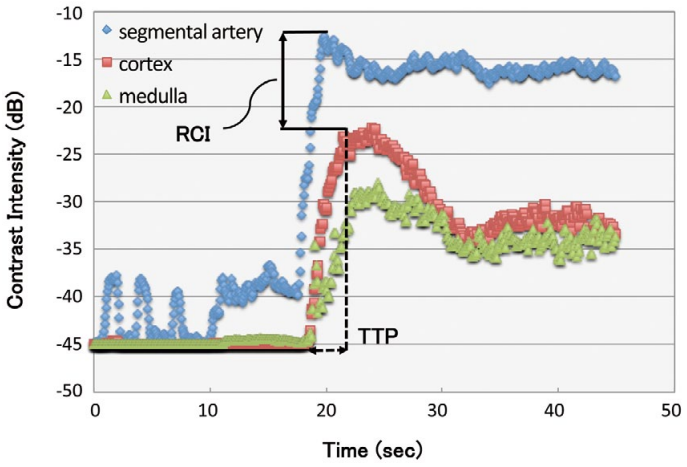

Figure 2. Representative time–intensity curve of a control generated from the average contrast intensity (CI) obtained in the region of interest. Time to peak intensity (TTP) was defined as the time from the initial rise to the peak. Relative CI (RCI) was calculated by subtracting the peak intensity in the segmental artery from that in the cortex and medulla.

required to have a stable breathing state that allowed for the long and reliable "breath holding" needed for CEUS. In all study patients, renal CEUS was performed before the treatment of CHF as a baseline inspection. When a patient's condition stabilized subsequent to all CHF treatments (e.g., oral and i.v. diuretics, vasodilators and digitalis preparations), echocardiography and renal CEUS were performed again as a post-treatment inspection. A second echocardiography confirmed that the pulmonary hypertension had improved and the TR was alleviated. Exclusion criteria included the presence of acute coronary syndrome, left-sided HF presenting with dyspnea or shock, uncontrolled high blood pressure, and renal artery stenosis, and chronic kidney disease ≥stage 4. In addition, 4 female patients (mean age, 53.7±15.2 years) with a history of breast cancer who required investigation of metastatic liver cancer on CEUS and 5 healthy volunteers were included as normal controls (4 women; mean age, 64.8±14.5 years). In the breast cancer patients, CEUS of the liver was continued after the end of the renal CEUS. The study protocol was approved by the institution ethics committee, and all subjects provided written informed consent prior to participating in the study.

Echocardiography

Comprehensive transthoracic echocardiography was performed according to published guidelines using commercially available ultrasound systems (Vivid E9 ultrasound machine; GE Healthcare UK, Little Chalfont, England). Based on the recommendations of the American Society of Echocardiography,[17] left ventricular ejection fraction (LVEF) was calculated using a modification of Simpson's equation. The degrees of mitral regurgitation and TR were evaluated based on published guidelines.[18] To estimate the right atrial pressure (RAP), the diameter of the IVC and its respiratory variations were measured.[19] The pulmonary artery pressure (PAP) was determined from the peak TR jet velocity, using the simplified Bernoulli equation and combined with an estimated RAP: $PAP=4(V)^2+RAP$, where V is the peak velocity of the TR jet. Pulmonary hypertension was defined as estimated PAP ≥40 mmHg.

Laboratory Data

Blood samples were taken on the same day as the echo-

Table 1. CHF Patient Clinical Characteristics and Medication

Patient ID no.	Age (years)	Gender	Diagnosis	Loop diuretics	Spironolactone	Tolvaptan	ACEI/ARB	β-blocker
1	77	F	AF tachycardia, mild MS	+	+	–	+	–
2	85	M	HFpEF	+	+	+	–	–
3	83	M	AF tachycardia, MR	+	+	+	+	+
4	85	F	HFpEF	+	+	–	+	+
5	81	M	MR	+	+	+	+	+
6	64	M	p/o MVR, p/o PMI	+	+	–	+	–
7	71	M	ICM	+	+	–	+	+
8	84	F	MR, TR	+	–	–	+	+
9	86	F	HFpEF	+	+	–	+	–
10	84	M	Myocardial amyloidosis	+	+	+	+	+
11	90	M	HFpEF	+	+	–	+	–

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CHF, congestive heart failure; HFpEF, heart failure with preserved ejection fraction; ICM, ischemic cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; p/o MVR, post mitral valve replacement; PMI, pacemaker implantation; TR, tricuspid regurgitation.

cardiographic studies. The creatinine-based estimated glomerular filtration rate (eGFR) was calculated using the Japanese coefficient-modified Chronic Kidney Disease Epidemiology Collaboration equation. For females, the product of this equation was multiplied by a correction factor of 0.742.[20]

CEUS

CEUS was performed using Aplio™MX and Aplio™i700 ultrasound diagnostic equipment (Canon Medical Systems, Otawara, Japan) with a 3.5-MHz convex probe. The kidneys were scanned using the lateral or translumbar subcostal approach with the patient in the supine position. B-mode and color Doppler scanning was initially performed for visualization within the renal cortex, medulla, and segmental arteries. After the bolus injection of Sonazoid™ (Daiichi-Sankyo, Tokyo, Japan) at 0.0075 mL/kg, image acquisitions was started using the phase inversion mode (transmitted/received at 1.8/3.6 MHz, respectively) at a dynamic range of 45 dB and an MI of 0.19–0.22, with the focus on the renal pelvis. Image acquisitions was initiated at the start of the contrast agent injection. The subjects were instructed to begin breath holding approximately 15 s after injection of the contrast agent during image acquisition.

CEUS Analysis

Digital cine loops were transferred to a PC system for offline quantification of CEUS. This analysis was performed using image analysis software (ImageLab; Canon Medical Systems). Oval-shaped regions of interest (ROI) were drawn over the middle superficial peripheral renal cortex, medulla, and segmental artery (**Figure 1**). The average contrast intensity (CI) was measured in dB, and the time-intensity curve (TIC) was generated from the average CI obtained in an ROI. The following parameters were measured on the TIC: time to peak (TTP; s), which reflects perfusion velocity, and relative CI (RCI), which is an estimate of renal parenchymal blood volume (**Figure 2**).[21] TTP was defined as the time from the initial rise to the peak. Given that ImageLab had no smoothing function for TIC, the curves were not smooth. For determining the peak, an average of 5 points from the first highest intensity was calculated on the TIC.

Statistical Analysis

Statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean±SD. Significant intergroup differences were estimated using the unpaired Student's t-test. A statistical significance threshold of 0.05 was applied throughout.

Results

Patients

The CHF patient baseline clinical characteristics and medication are summarized in **Table 1**. Approximately half of the subjects had valvular disease, 36% had HF with preserved ejection fraction, and 82% had atrial fibrillation. The changes in the cardiac and renal function index, the degree of valvular regurgitation, and the IVC diameter after treatment are summarized in **Table 2**. Under standard CHF treatment, loop diuretics were given to all patients and spironolactone to 91% of the patients. Tolvaptan was given to 36% of patients. After treatment, the CHF symptoms promptly improved.

Quantitative Analysis of Renal Perfusion

In controls, approximately 15 s after injection, the contrast agent was first visible at the renal hilum and propagated to the interlobar and arcuate arteries and then to the renal cortex. Enhancement spread from the cortex to the margin of the medulla and then to the center. Each TIC consisted of a prominent ascending slope, a peak, and a descending slope that plateaued. The ascending slope was steep and gradually descended after peaking (**Figure 2**). The TTP and RCI in the controls and at baseline and after treatment in all CHF patients are shown in **Figure 3**. In the CHF patients, the TTP at baseline was significantly prolonged compared with that in the controls (cortex, 10.8±3.5 vs. 4.6±1.2 s, P<0.0001; medulla, 10.6±3.0 vs. 5.1±1.6 s, P<0.0001), and the RCI was lower in the controls (cortex, −16.5±5.2 vs. −8.8±1.5 dB, P<0.0001; medulla, −22.8±5.2 vs. −14.8±2.4 dB, P<0.0001). Representative CEUS and TIC of a CHF patient before and after treatment are shown in **Figures 4**,**5**. The time required for parenchymal enhancement at baseline was longer than that required after treatment. The maximum intensities in the parenchyma at baseline were reduced

Table 2. Change in Cardiac and Renal Function After Treatment in CHF Patients

Patient ID no.	eGFR (mL/min/1.73 m²)		LVEF (%)		Hematocrit (%)		PAP (mmHg)	
	Baseline	After treatment	Baseline	After treatment	Baseline	After treatment	Baseline	After treatment
1	59.9	54.9	60	73	34.3	41.4	62	25
2	47.9	59.4	76	78	30.6	27.0	69	53
3	58.4	62.8	46	41	37.3	35.7	56	19
4	81.9	62.1	51	65	41.8	40.0	70	44
5	40.6	36.6	33	31	39.7	44.6	64	29
6	52.9	65.2	28	34	31.0	37.4	48	27
7	79.4	79.4	23	30	36.0	33.8	45	20
8	55.9	46.8	71	69	32.2	32.7	82	70
9	73.8	53.1	66	70	31.1	30.8	54	26
10	65.8	51.6	35	55	37.8	30.7	64	40
11	52.2	52.2	63	73	28.4	34.0	48	36

Patient ID no.	TR grade		MR grade		IVC (mm)	
	Baseline	After treatment	Baseline	After treatment	Baseline	After treatment
1	Severe	Mild	Severe	Mild	21	11
2	Severe	Mild	Mild	Mild	24	21
3	Moderate	Mild	Severe	Moderate	27	21
4	Severe	Mild	Moderate	Mild	17	10
5	Moderate	Mild	Severe	Mild	24	11
6	Moderate	Mild	None	None	31	17
7	Moderate	None	Mild	None	24	15
8	Severe	Severe	Severe	Moderate	18	17
9	Moderate	Mild	Moderate	Mild	18	8
10	Moderate	Mild	Moderate	Mild	22	21
11	Severe	Mild	Mild	Mild	23	16

eGFR, estimated glomerular filtration rate; IVC, inferior vena cava; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure. Other abbreviations as in Table 1.

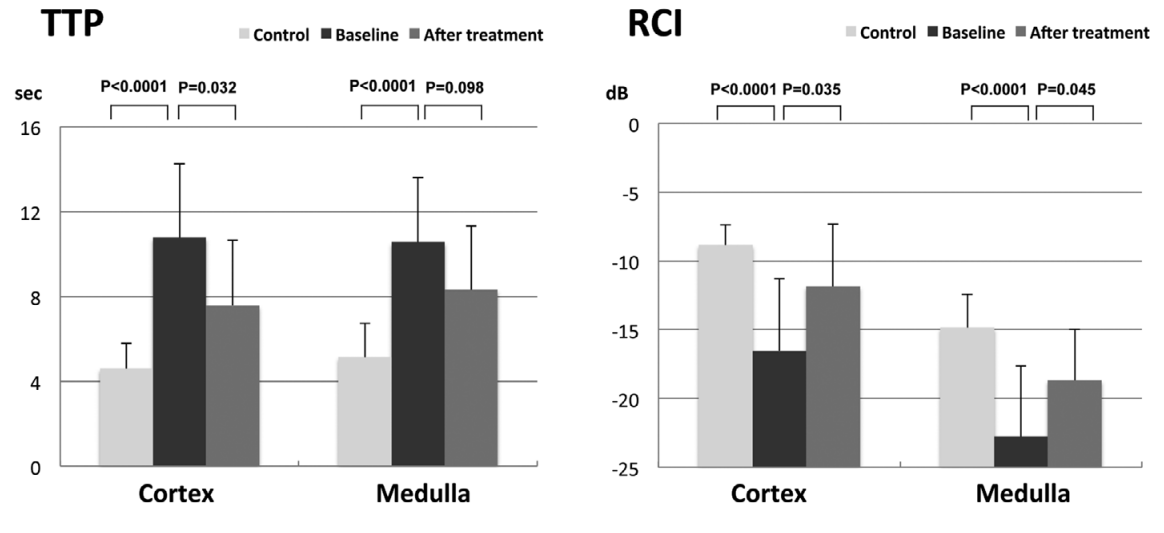

Figure 3. Change in time to peak intensity (TTP) and relative contrast intensity (RCI) after treatment in congestive heart failure patients, relative to controls.

compared with those after treatment. On the TIC, the ascending slopes in the cortex and medulla at baseline were both less steep than those after treatment. As the parenchymal contrast intensity rose, the RCI increased after treatment. As shown in **Figure 3**, the RCI was significantly increased in CHF patients after treatment (cortex, −16.5±5.2 to −11.8±4.5 dB, P=0.035; medulla, −22.8±5.2 to −18.7±3.7 dB, P=0.045). Although the TTP in the cortex decreased after treatment (10.8±3.5 to 7.6±3.1 s, P=0.032), it was not altered in the medulla (10.6±3.0 to 8.3±3.2 s, P=0.098).

Discussion

To our knowledge, this study is the first to evaluate renal congestion on renal perfusion CEUS in CHF patients and normal controls. Furthermore, renal congestion was compared before and after treatment in CHF patients. TIC analysis indicated impaired renal parenchymal flow, and the TTP suggested prolonged perfusion rates of the renal parenchyma at baseline in CHF patients. RCI, which is a measure of renal blood volume, was also decreased at baseline in CHF patients. Trends suggesting improvement in these indices were observed after CHF treatment. The changes in these indicators are likely due to the improvement in renal congestion.

Renal Congestion in CHF Patients

In this study, although CVP could not be measured invasively, echocardiography showed that the IVC was expanded, estimated PAP was high, and TR was significant in CHF patients (**Table 2**). This suggests that CVP was elevated before treatment and that renal congestion was present. We attempted to indirectly estimate the presence of renal congestion by evaluating renal perfusion. Intrarenal vascular impairments due to renal parenchymal disorders, such as renal sclerosis, should not change with acute HF treatment alone, but intrarenal vessel collapse due to increased renal interstitial pressure may improve if renal congestion is resolved. The change in the perfusion index during the short treatment period was suspected to be the cause of renal congestion.

In some cases, eGFR did not improve even after CHF treatment, although hematocrit tended to increase in patients whose eGFR decreased after treatment. Aggressive decongestion was recently found to be associated with improved clinical outcomes despite the deterioration in renal function during therapy for acute HF.[22–24] Hence, we suggest that eGFR alone cannot accurately evaluate renal dysfunction as a result of renal congestion; in this respect, imaging methods such as CEUS are essential for establishing a clinical diagnosis.

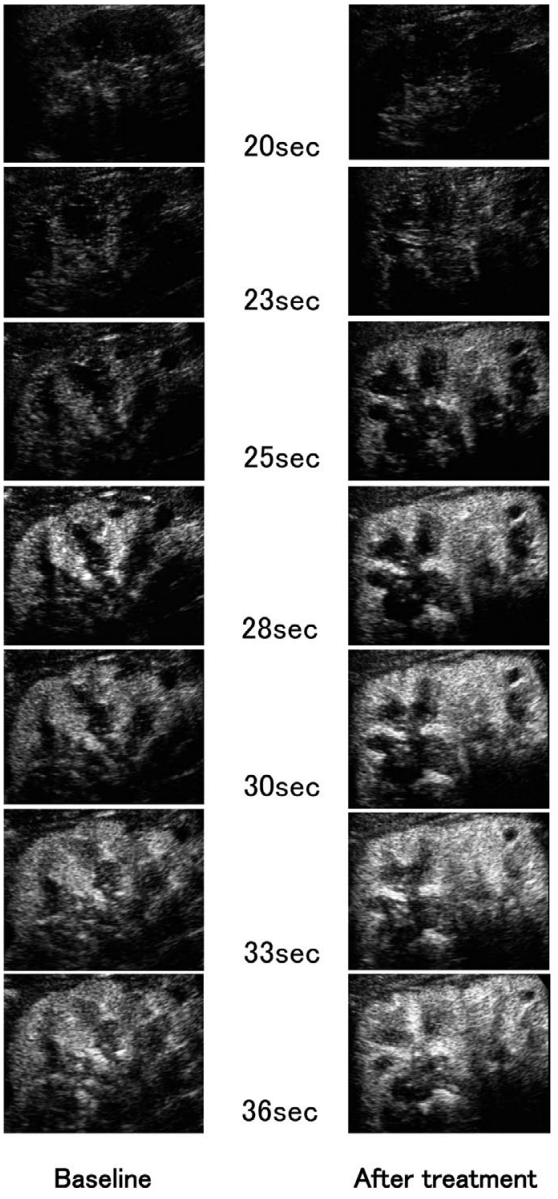

Figure 4. Serial contrast-enhanced ultrasound in a representative congestive heart failure patient at baseline and after treatment. The time required for parenchymal enhancement at baseline was longer than that after treatment. Maximum intensity in the parenchyma was lower at baseline than after treatment.

CEUS

CEUS with Sonazoid® allowed the non-invasive assessment of renal perfusion in the clinical setting.[25–27] Microbubbles are smaller than red blood cells and traverse the lungs from the venous to the arterial system and can be imaged within the capillary beds of the target organ. Parenchymal contrast imaging is based on the blood flow rate in the distal renal vessels. The TIC shows the time from when the contrast agent begins to flow into the parenchyma until it peaks, while the TTP reflects the perfusion velocity to the organ and the peak intensity reflects the amount of blood per unit volume.[28–31] The intensity, however, is dependent on acoustic pressure and is influenced by the heterogeneity of the acoustic field. Yamada et al reported that a novel quantitative method could overcome acoustic field heterogeneity in the evaluation of myocardial perfusion during human myocardial contrast echocardiography. Using their method, the blood volume fraction per unit volume was estimated by adjustment of the signal intensity of the myocardium with that of the left ventricular cavity.[21] Using this quantitative method in the current study, the blood volume of the renal parenchyma was estimated using the intensity of the neighboring segmental arteries as a reference.

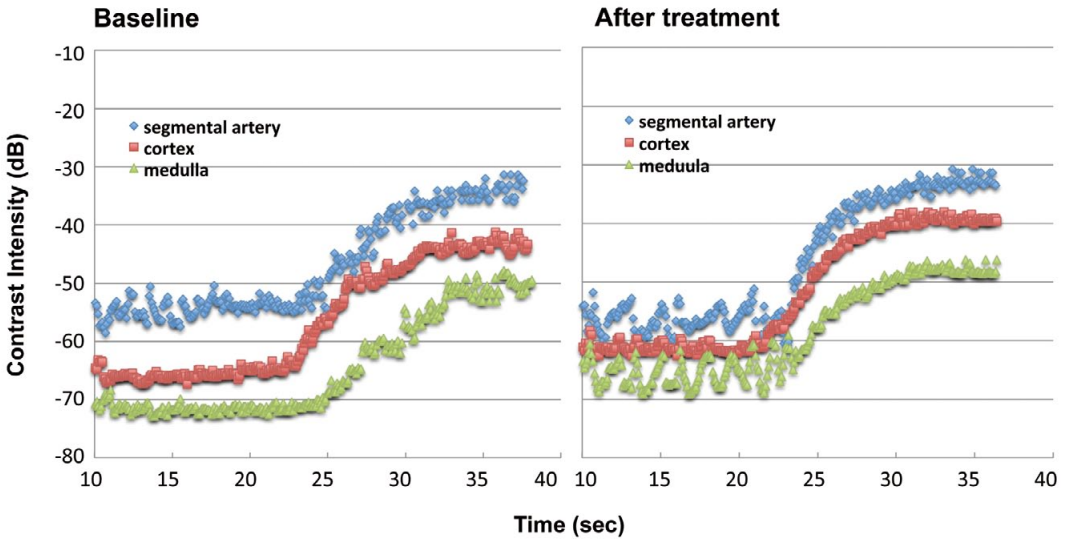

Figure 5. Change in time-intensity curve in a congestive heart failure patient after treatment.

Renal Perfusion Impairment in CHF Patients

There are 2 possible mechanisms for perfusion impairment of the renal parenchyma in obvious right-sided HF accompanying increased CVP. First, in renal congestion, the renal hypertension caused by elevated CVP in CHF patients could cause fluid leakage into the renal interstitium, which can increase renal interstitial pressure and decrease renal perfusion pressure, both of which decrease glomerular filtration.[32] Given that the kidney is a capsule organ, intrarenal pressure is easily increased by interstitial congestion. Thus, the intrarenal vessels are thus easily collapsed by the increased renal interstitial pressure and show decreased compliance around the renal vessel due to edema of the renal parenchyma. We recently reported the results of animal experiments demonstrating that renal parenchymal perfusion disturbances using CEUS in the context of acute renal congestion are accompanied by increased renal interstitial pressure. These animal experiments showed that renal perfusion was impaired as the CVP and renal interstitial pressure increase.[15] Similar to the experimental results, the TTP in CHF patients before treatment was significantly prolonged in this study. In the cortex, the TTP was shortened due to the improvement in renal congestion after CHF treatment; this indicates that the perfusion rate of the renal parenchyma was decreased as a result of renal congestion. Second, influences of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) must be considered. In CHF patients, increased activation of the sympathetic nervous system causes renal vasoconstriction; in particular, the splanchnic veins are controlled by the sympathetic vascular tonus.[33,34] Although the flow rate was prolonged in the previously noted animal experimental model, the decline in the blood volume index was not significant. In the present study, however, the flow rate and the blood volume were markedly impaired in CHF patients before treatment. TTP on CEUS reflects the blood inflow rate in the arterial phase, whereas RCI reflects the blood volume of the microvascular bed containing the venous phase. We speculate that the hypovolemia in the microvascular bed was due to both the increased interstitial pressure and the spasm of the peripheral blood vessels by sympathetic nerve activation. Given that the aforementioned animal experiment represented an acute model, delays in the flow rate occurred rapidly due to pressure increase in the interstitium, but because vasospasm caused by sympathetic nervous system activation did not occur in the acute phase, the blood volume did not decrease. In contrast, peripheral vasospasm is marked in human HF.

Differences Between the Cortex and Medulla

The advantage of CEUS is that perfusion of the cortex and medulla of the renal parenchyma can be individually evaluated. Because >90% of blood flow entering the kidney supplies the renal cortex,[35] the medulla has a much less extensive blood vessel distribution. Furthermore, medullary circulation is poorly autoregulated and is very sensitive to small increases in vasa recta capillary pressure and renal interstitial fluid pressure.[36,37] In our previous animal experiments, perfusion impairment due to acute renal congestion was more pronounced in the medulla than in the cortex.[15] Therefore, in the assessment of renal congestion, evaluation of the medullary circulation may be more important than evaluation of the cortical circulation. In the present study, improved blood volume was observed in the cortical and medullary regions, and the perfusion rate of the cortex was restored after CHF treatment. The perfusion rate in the medulla, however, did not change significantly with treatment. We speculated that the remaining renal congestion in the medulla and the persistence of contraction of the vasa recta were due to the original renal dysfunction. This may have been more extensively influenced by improvements in perfusion impairment after CHF treatment than the cortex, which is rich in blood vessels and has a highly developed autoregulatory system. Renal perfusion, however, is likely affected by cardiac output or arteriosclerosis in renal blood vessels. Although further examinations are needed at this point, this method may facilitate assessment of the persistence of renal congestion after treatment and determination

of the amount of diuretics required.

Imaging of Renal Congestion

There are very few reports on the use of diagnostic imaging for the purpose of assessing renal congestion. Iida et al reported that the intrarenal venous flow pattern on intrarenal Doppler ultrasonography was associated with mean RAP in CHF patients.[6] They mentioned that there are likely 2 mechanisms: renal congestion due to RAP elevation, which is in afterload to the intrarenal vein; and significant TR. While the intrarenal venous flow was evaluated in their study, in the present study, perfusion failure during blood filling into the peripheral vascular bed of the renal parenchyma was imaged. Renal congestion increased the pressure in the renal interstitium, and the collapse of blood vessels in the kidney may impair renal perfusion. Furthermore, because the contrast method we used can evaluate the renal medulla and cortex separately, it is possible to evaluate differences due to the location of the renal perfusion.

In rat models of hypertensive HF, Chiba et al evaluated renal medullary perfusion using intrarenal Doppler and CEUS and compared these results with histology.[38] In the HF rat models, the interstitial pressure in the renal medulla was increased, and CEUS showed that TTP was prolonged,[38] findings that are in agreement with the present results. Furthermore, Chiba et al reported that renal fibrosis was caused by renal congestion and that the inhibition of renal congestion by tolvaptan was associated with a renoprotective effect.[38] In the present study, renal fibrosis was 1 potential reason why TTP improvement in the renal medulla was not significant, even after improvement in the primary HF symptoms. Further studies are needed to determine the effects of drugs, such as tolvaptan, on renal congestion in human subjects.

Relationship to Previous Quantitative CEUS

Several quantitative methods have been reported for the assessment of renal tissue perfusion.[39–42] Wei et al utilized a replenishment curve (the TIC) of inflowing bubbles after destruction of all bubbles in the acoustic field with a high MI ultrasound burst during the continuous injection of a contrast agent; these replenishment curves were fitted to the exponential function: $y=A(1-e^{-\beta t})$.[42] In this method, A represents the blood volume in the plateau and β represents the mean microbubbles velocity. It may be true that β or A more accurately reflects the perfusion rate and renal blood volume than the present method, but that method requires an ultrasound contrast agent suitable for continuous i.v. injection and appropriate software for creating the replenishment curve, tools that are not always available in clinical situations. Therefore, a simple conventional quantitative method of measuring TTP and the peak TIC intensity using the bolus injection of a contrast agent has been reported to be suitable for clinical application.[28,29,31] Some current ultrasound devices, however, include software that automatically creates a TIC; using these devices, the effect of CEUS is also improved. Using these techniques, the area under the curve of the TIC can be easily measured, and the TTP and peak intensity can be more objectively identified. Unfortunately, at the time and location of the current study, these devices were not commonly available, hence further studies using more accurate quantification methods involving such software may be necessary.

Study Limitations

This study has several limitations. First, in this small sample size study, cases of HF with preserved ejection fraction and those of HF with reduced ejection fraction were mixed. Second, subjects with different LVEF and cardiac outputs were standardized, and control patients in this study had a different average age than CHF patients. Differences in renal perfusion due to these reasons could not be ruled out. Third, the subjects included patients with mild to moderate renal dysfunction. The aim of this study, however, was to examine renal perfusion injury due to renal congestion in subjects without renal dysfunction; thus, the original effects of renal dysfunction cannot be excluded. Fourth, we did not measure hemodynamic data, including CVP, but all patients had obvious symptoms of right-sided HF and IVC dilation without inspiratory collapse, which was confirmed on echocardiography. CVP before treatment may have been high in the present subjects. Fifth, because these subjects were undergoing routine clinical treatment, the amount and type of diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers used were not uniform. These medications can potentially affect renal congestion but, because the number of subjects was low in this study, this issue could not be resolved. Additionally, this study was unable to elucidate whether these medications influenced renal perfusion. Finally, hormone factors influencing the sympathetic nervous systems and RAAS were not evaluated.

Conclusions

CEUS showed renal perfusion impairments that may be associated with increased renal interstitial pressure due to renal congestion in CHF patients. CEUS is a unique method that allows the non-invasive independent assessment of renal perfusion in the cortex and medulla and may assist in clinical evaluation of renal pathophysiological changes that occur in renal congestion in CHF patients.

Disclosures

The authors declare no conflicts of interest.

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