Successful Depressor Effect Concomitant with Complete Normalization of High Renin and Aldosterone Profile by Percutaneous Transluminal Renal Angioplasty in a Patient with Acute Exacerbated Heart Failure with Preserved Ejection Fraction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 59
Final Diagnosis: Renovascular hypertension
Symptoms: Dyspnea
Medication: —
Clinical Procedure: Percutaneous transluminal renal angioplasty
Specialty: Cardiology

Objective: Unusual or unexpected effect of treatment
Background: Although the effect of percutaneous transluminal renal angioplasty (PTRA) on clinical outcomes has not been established in previous clinical studies, some case reports showed that PTRA drastically improved patient outcomes. The appropriateness of PTRA should be discussed in detail.
Case Report: A 59-year-old man had been on treatment for hypertension for 5 years, but his blood pressure (BP) had been poorly controlled for the past 5 months. He was hospitalized for pulmonary edema due to heart failure with preserved ejection fraction (HFpEF). During hospitalization, ultrasound and plain computed tomography revealed atrophy of the right kidney, and laboratory investigations indicated secondary aldosteronism with high plasma renin activity (PRA). Unenhanced magnetic resonance imaging (MRI) suggested severe stenosis or occlusion of the right renal artery. PTRA was performed for total occlusion at the origin of the right renal artery, resulting in favorable dilation of the vessel and good blood flow.
A differential renal vein renin assay showed a right-left difference of PRA before PTRA, but this disappeared after the procedure. Both PRA and the plasma aldosterone concentration were normalized after PTRA. In addition, the patient's BP decreased, proteinuria was reduced, diuretics could be discontinued, and his calcium channel blocker dosage was decreased.
Conclusions: The present case suggests that screening for renal artery stenosis by unenhanced MRI may be useful in patients who have HFpEF because PTRA can be used to achieve marked improvement of hypertension, endocrine abnormalities, and heart failure if stenosis is detected.

MeSH Keywords: Angioplasty • Hypertension • Magnetic Resonance Angiography • Renal Artery Obstruction

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Background

Renal artery stenosis (RAS) causes renal hypoperfusion and activation of the renin-angiotensin-aldosterone system (RAAS), resulting in elevated blood pressure (BP), congestive heart failure, and renal dysfunction. Treatment of this disease is By medical therapy, mainly with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and percutaneous transluminal renal angioplasty (PTRA) may be performed concomitant with medical therapy. However, PTRA for RAS did not affect the cardiovascular prognosis and renal function in 2 large-scale trials – the Angioplasty and STent for Renal Artery Lesions (ASTRAL) study [1] and the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study [2].

Although the ASTRAL trial enrolled patients with at least 50% renal artery stenosis, hemodynamic assessment was not conducted and renal ischemia was not validated. The CORAL trial excluded patients with intractable hypertension, exacerbation of renal dysfunction, and recent onset of heart failure (≤3 months) (i.e., patients who are generally considered suitable for PTRA). Some reports showed that PTRA drastically improved patient outcomes [3,4]. The purpose of this case report is to discuss in detail the appropriate indications of PTRA and screening for RAS.

Case report

Patient: A 59-year-old man.

Chief complaint: dyspnea.

History of the present illness: at the age of 54 years, hypertension was diagnosed during hospitalization for intestinal obstruction.

Treatment was started with a calcium channel blocker and an angiotensin II receptor antagonist, and thereafter his BP was well controlled.

At the age of 59 years, his systolic blood pressure (SBP) increased to about 170 mmHg and BP was poorly controlled for several months. His serum creatinine increased from 0.8 mg/dl to 1.6 mg/dl during a 3-month period. The patient developed exertional dyspnea, which gradually became worse.

He was transported to our hospital by ambulance due to the onset of respiratory distress at rest. Echocardiography indicated that left ventricular systolic function was maintained, but a chest X-ray film demonstrated cardiac enlargement and pulmonary congestion. A diagnosis of pulmonary edema due to heart failure with preserved ejection fraction (HFpEF) was made and he was urgently admitted to the hospital.

His past medical history included pulmonary embolism and pericarditis in his 30s. There was no special mention of his family history. His social history showed that he smoked 20 cigarettes a day for 40 years and had consumed 44 g of alcohol a day.

Physical examination on admission revealed height 163 cm and weight 49 kg, blood pressure was 174/124 mmHg, and heart rate was regular and 89/min. His heart sound showed no murmur. A lung examination showed an increased respiratory rate (28/min) and wheezes at the end of exhalation in both lungs. No peripheral edema or hepatomegaly were observed.

Immediately after admission, he was treated with intravenous furosemide, as well as carperitide (0.025 γ) and noninvasive positive pressure ventilation. Diuresis was rapid and his respiratory condition became stable. Since the patient had hypertension and circumferential cardiac enlargement on echocardiography, hypertensive heart disease was suspected. After admission, he received multiple antihypertensive agents (nifedipine CR at 60 mg/day, telmisartan at 20 mg/day, furosemide at 40 mg/day, and spironolactone at 50 mg/day), but his BP remained around 150/90 mmHg and was not sufficiently controlled.

The patient had renal dysfunction and hypokalemia (2.5 mmol/L). Further tests on admission demonstrated secondary aldosteronism associated with high plasma renin activity (PRA) (Table 1). Consequently, renovascular hypertension was suspected due to uncontrolled hypertension, hypokalemia, high PRA and aldosterone, progressive renal dysfunction, and heart failure. Ultrasound and plain computed tomography (CT) (Siemens, Munich, Germany) were performed, detecting unilateral renal atrophy. Due to the patient's renal dysfunction, unenhanced magnetic resonance imaging (MRI) (Philips, Amsterdam. Netherlands) (Figure 1) was performed to evaluate the renal arteries rather than contrast CT, revealing severe stenosis or occlusion at the origin of the right renal artery and the right renal atrophy.

On hospital day 17, selective renal angiography was conducted via the left radial artery, confirming total occlusion at the origin of the right renal artery. The location of the right renal artery was identified by CT and MRI relative to the position of the left renal artery, and a stump was detected at the occlusion site. Accordingly, it was considered that blood flow could be restored and PTRA was performed (Figure 2).

A 6F guiding catheter (JR4.0; Medikit Co., Tokyo, Japan) was positioned at the ostial part of the right artery. A 0.014-inch guide wire (Aguru™ floppy; Boston Scientific Corporation, Marlborough, USA) and a microcatheter (Prominent, Tokai Medical Products Inc., Kasugai, Japan) were used to cross the occlusion, after which the microcatheter was advanced to the

Table 1. Laboratory findings on admission.

| Test	Value	Ref. range	Test	Value	Ref. range
WBC (10³/µl)	10.2	(3.3–8.6)	LDL–C (mg/dL)	225	(65–163)
Hb (g/dl)	11.2	(13.7–16.8)	CRP (mg/dL)	0.21	(<0.14)
PLT (10⁴/µl)	28.4	(15.8–34.8)	TSH (µIU/mL)	5.59	(0.43–4.83)
Alb (g/dl)	2.4	(4.1–5.1)	FT4 (ng/dL)	1.47	(0.87–1.72)
AST (U/L)	21	(13–30)	NTproBNP (pg/mL)	14137	(<125)
ALT (U/L)	16	(10–42)	Urinary protein	10.3	(g/gCr)
LDH (U/L)	257	(124–222)	Active plasma renin (ng/(mL h)	68	(0.3–2.9)
CK (U/L)	194	(59–248)	Plasma aldosterone (pg/mL)	756	(29.9–159)
BS (mg/dL)	185	(73–109)	Plasma adrenaline (pg/mL)	38	(<100)
HbA1c (%)	5.7	(4.6–6.2)	Plasma noradrenaline (pg/mL)	719	(100–450)
BUN (mg/dL)	22	(8–20)	Plasma dopamine (pg/mL)	21	(<20)
Cr (mg/dL)	1.6	(0.7–1.1)	ACTH (pg/ml)	49.1	(7.2–66.3)
			Plasma cortisol (µg/dL)	18.0	(6.24–18)

WBC – white blood cell count; Hb – hemoglobin; PLT – platelets; Alb – albumin; AST – aspartate transaminase; ALT – alanine transaminase; LDH – lactate dehydrogenase; CK – creatine kinase; BP – blood pressure; HbA1c – hemoglobin A1c; BUN – blood urea nitrogen; Cr – creatinine; LDL – low-density lipoprotein; CRP – C-reactive protein; TSH – thyroid-stimulating hormone; FT4 – free thyroxine; NTproBNP – N-terminal pro-brain natriuretic peptide; ACTH – adrenocorticotropic hormone.
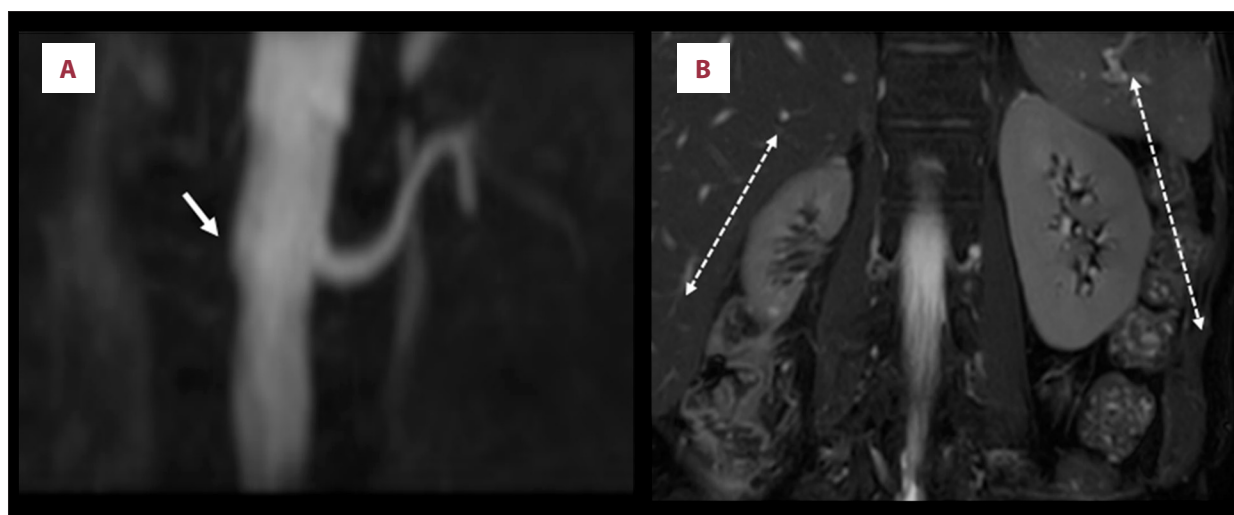

Figure 1. Unenhanced MRI (Balanced-TFE, Philips). (**A**) Total occlusion at the origin of the right renal artery. (**B**) Atrophy of the right kidney (right: 6.8 cm, left: 10.2 cm).

distal part of the renal artery and back flow of blood was verified. Then, tip imaging was conducted, and it was confirmed that the wire was in the lumen of the main trunk of the renal artery. To treat the lesion, a 2.0×20 mm balloon (Shiden; Kaneka Medical Products, Osaka, Japan) was inflated and then exchanged for a larger balloon. Subsequently, a 4.0×15 mm cutting balloon (Peripheral Cutting Balloon, Boston Scientific) was used to achieve additional dilation. Finally, a 5.0×19 mm stent (Express™ Vascular SD; Boston Scientific) was placed to

fully cover the lesion from the entry site. The occlusion improved to 0% stenosis and there was no distal embolism or renal artery perforation (Figure 2). Selective collection of renal vein blood for measurement of PRA was done before and after release of renal artery occlusion during PTRA. Before PTRA, PRA was significantly higher in the right renal vein compared with the left renal vein, while the right-left difference disappeared 15 min after the procedure (Figure 3).
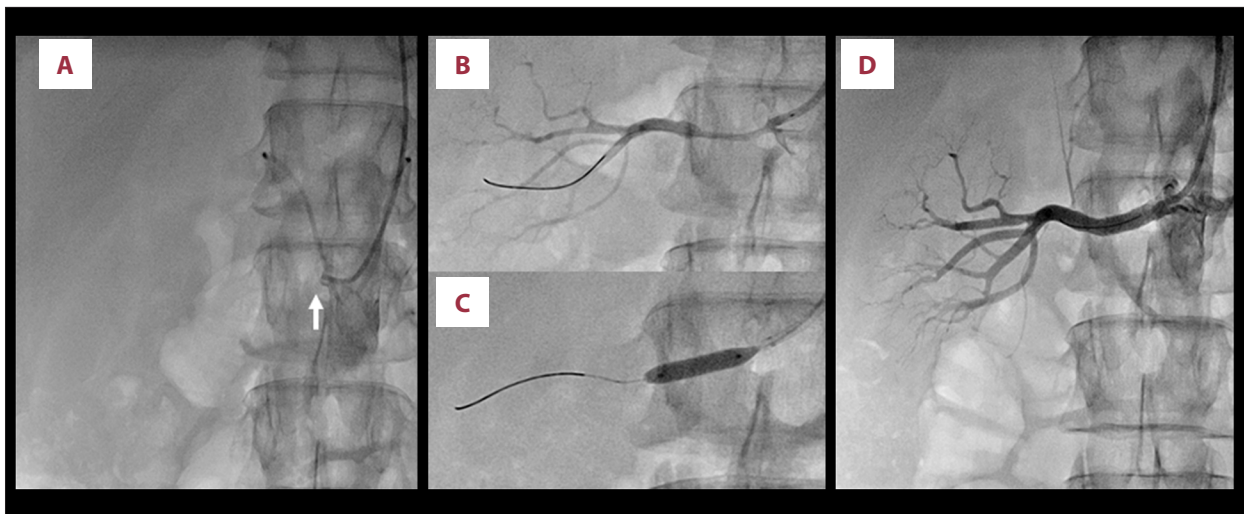
Figure 2. Percutaneous transluminal renal angioplasty procedure. (**A**) Selective right renal angiography. There is total occlusion at the origin of the right renal artery. (**B**) The lesion was dilated with a small-diameter balloon and blood flow was restored. (**C**) A cutting balloon was used to increase dilation of the lesion. (**D**) A stent (Express: 5.0×19 mm) was placed with 2 mm protruding into the aorta. Good expansion of the right renal artery stenosis was achieved.
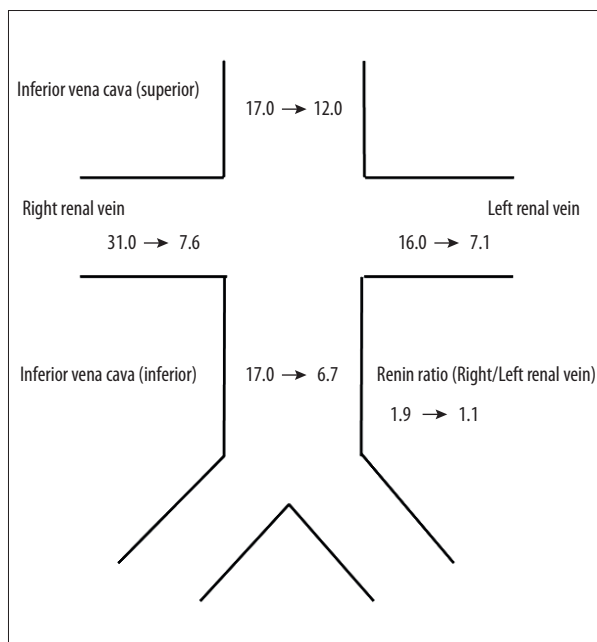
Figure 3. Renal vein plasma renin activity before and after PTRA. PTRA – percutaneous transluminal renal angioplasty.

To protect the kidney, intravenous fluid infusion was conducted from 1 day before PTRA to postoperative day 4, and continuous hemodiafiltration was performed for 2 days after PTRA. Good diuresis (4000 ml/day) was achieved after PTRA, with no deterioration of renal function, and proteinuria also decreased (Figure 4).

Immediately after PTRA, the dose of nifedipine was decreased from 60 mg/day to 20 mg/day, while furosemide and spironolactone were discontinued on day 8 after the procedure (Figure 4). Control of the patient's BP was markedly improved by the procedure (Figure 4). At 1 week after PTRA (1 week after completion of fluid infusion), mean SBP was significantly lower than at 1 week before PTRA, with morning SBP decreasing from 145/93 mmHg to130/78 mmHg and evening SBP decreasing from 140/83 mmHg to 120/72 mmHg (both $p<0.05$).

PRA and the plasma aldosterone concentration decreased dramatically after PTRA (Figure 5). After discontinuation of the aldosterone antagonist, the potassium level remained within normal range. The patient was discharged from hospital on hospital day 30. Both home and office BP have been controlled at around 130/80 mmHg for approximately 6 months since discharge.

Discussion

Summary

We treated a patient who demonstrated marked improvement of renal vascular hypertension due to renal artery occlusion after undergoing PTRA. This patient was considered to have cardiac disturbance syndrome, as indicated by heart failure induced by marked activation of the renin-angiotensin-aldosterone system (RAAS) as a consequence of ischemic nephropathy resulting from renal arterial stenosis. After PTRA, his BP decreased significantly, the dosages of his antihypertensive drugs were decreased, and RAS profile was normalized.
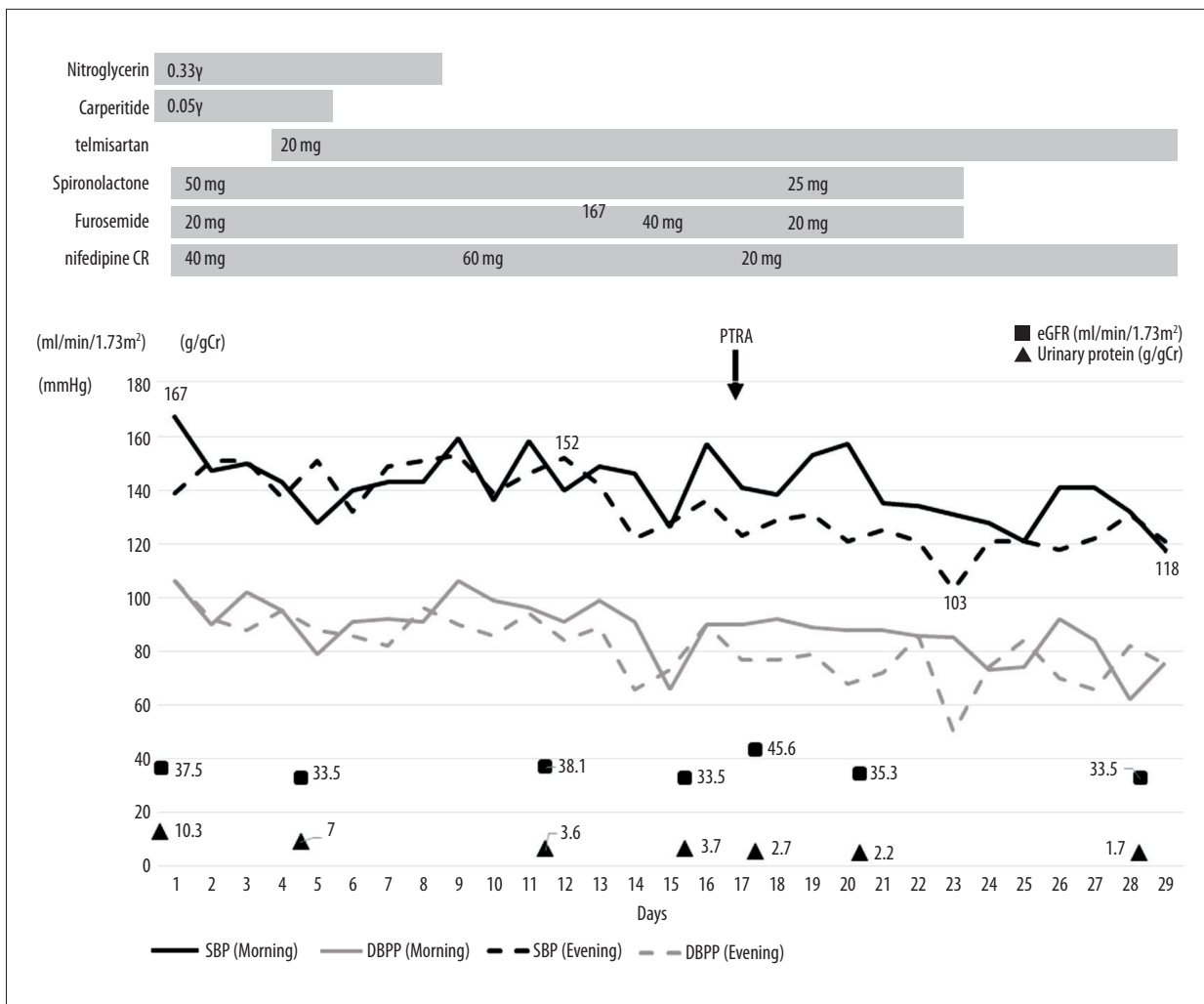
Figure 4. Changes of blood pressure and renal function on admission. SBP – systolic blood pressure; DBP – diastolic blood pressure, eGFR – estimated glomerular filtration rate.

	Before	5 days later	13 days later	26 days later
Active plasma renin (ng/(mL h)	68	<0.1	0.4	0.3
Plasma aldosterone (pg/mL)	756	28.2	90.5	54.2

Figure 5. Changes in plasma renin activity and the plasma aldosterone concentration after PTRA. PTRA – percutaneous transluminal renal angioplasty.

Application

Before performing PTRA, it is important to evaluate whether it is suitable from both the pathophysiological and anatomical perspectives. Suitable pathophysiological findings include worsening hypertension and renal function, heart failure of unknown etiology, and endocrine abnormalities such as hyperreninemia causing hypokalemia. Hemodynamic assessment should be performed to determine the anatomical severity of

stenosis, including the peak systolic velocity and renal aortic ratio measured by renal artery Doppler ultrasound and the catheter-based fractional flow reserve [5]. When the stenosis is ≥70%, both renal blood flow and renal perfusion pressure will be decreased [6].

Our patient had total occlusion of the right renal artery associated with right kidney atrophy, and we carefully evaluated whether PTRA was likely to be effective prior to intervention. From the pathophysiological viewpoint, the presence of heart failure, endocrine abnormalities such as high renin aldosteronism and hypokalemia, and poor BP control despite ≥3 medications (including diuretic) suggested a cardiac disturbance syndrome [7].

From the anatomical perspective, the patient had total occlusion of the right renal artery causing renal ischemia, suggesting that PTRA was appropriate, but renal atrophy was present,

so revascularization by PTRA would be less beneficial if the lesion was a chronic total occlusion. However, chronic renal artery stenosis causes fluid retention and volume overload that is reported to result in hyporeninemia. In contrast, the duration of occlusion is shorter (7.5 months on average) if a patient has hyperreninemia [8]. Since our patient had marked hyperreninemia, the duration of renal artery occlusion was expected to be shorter (subacute occlusion). Elevation of BP and progression of pulmonary edema over several months before admission supported this diagnosis. Finally, there was no calcification of the lesion, and a low tip weight 0.014 wire passed through it relatively easily, further supporting the diagnosis of subacute thrombotic occlusion.

Differential renal vein renin assay

The differential renal vein renin assay is the ratio of PRA in the affected renal vein by RAS to PRA in the contralateral renal vein sampled by catheter. When the ratio is 1.5 or more, it can be judged as hemodynamically significant RAS. The differential renal vein renin assay was conducted before and after PTRA, revealing a right-left difference just before the procedure, which demonstrated excessive renin secretion by the right kidney. In contrast, venous renin levels were comparable between the left and right renal veins immediately after PTRA, showing improvement of abnormal RAS activation. There have been no previous reports of renal vein renin levels immediately before and after PTRA in a patient with total renal artery occlusion. It is noteworthy that PRA decreased about 15 min after PTRA in this patient, and RAS-mediated cardiac disturbance syndrome due to renal artery occlusion was successfully ameliorated.

Renal function

There are several reports that about 1/4 of patients showed improved renal function following PTRA, while there was no improvement in 1/2 and exacerbation in 1/4 [9,10]. This suggests that renal function should be monitored carefully following PTRA.

In the present patient, the fluid infusion volume and dose of contrast medium for PTRA were decreased, and continuous hemodiafiltration was conducted immediately after the procedure. There was no change in eGFR after PTRA, and proteinuria decreased.

When PTRA is performed, contrast medium is injected directly into the kidneys of patients with chronic renal disease. To prevent contrast-induced nephropathy, sufficient infusion of fluid should be done before intervention, and the contrast medium should be diluted with physiological saline as appropriate during imaging. In some cases, continuous blood purification

should be considered to protect the kidney from contrast-induced nephropathy [11].

Heart failure

In patients with heart failure, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers inhibit myocardial fibrosis and proteinuria through suppression of RAAS. These drugs may be used to treat heart failure associated with ischemic nephropathy. However, renal perfusion pressure is decreased if these medications are used inappropriately, leading to iatrogenic exacerbation of renal impairment.

Improvement of renal ischemia through revascularization may help to improve the tolerability of these medications and provide secondary cardio-renal protection.

It is known that heart failure is often associated with renal impairment [12,13], and renal artery stenosis was reported to exist in 8–54% of patients with heart failure [14–16]. Thus, it is possible that patients with heart failure and renal impairment have underlying renal artery stenosis that induces ischemic nephropathy and RAAS activation, leading to heart failure. However, such patients cannot undergo contrast CT scanning due to their renal impairment, which can make renal artery stenosis difficult to investigate. It is possible that there are many patients with renal artery stenosis among those with HFpEF. Accordingly, PRA and plasma aldosterone concentration should be measured, and imaging to screen the renal artery should be routinely conducted. A common cause of renal artery stenosis is age-related atherosclerosis, and the pathologic changes progress with advancing age. Screening for renal artery stenosis should be done earlier in patients with heart failure, and the need for revascularization should be evaluated. Renal artery stenosis that is not associated with renal ischemia should also be followed up.

Diagnostic imaging

In the present patient, unenhanced MRI was a useful screening method for renal artery stenosis. Screening for renal artery stenosis is generally done with ultrasound, contrast CT, or contrast/non-contrast MRI. Renal artery ultrasound is non-invasive and is quite useful for functional evaluation of stenosis. However, the number of sonographers with experience in renal artery ultrasound is limited and it is not an easy examination to perform, with the results being significantly influenced by the sonographer's technique and the patient's visceral obesity. Since renal artery blood flow is evaluated, good visualization may not be possible in the presence of an accessory renal artery or total occlusion.

CT shows superior sensitivity and specificity to ultrasound, but adverse reactions such as contrast allergy and renal impairment

are drawbacks. Moreover, patients with cardiovascular disease often have renal impairment and are not suitable for CT screening, as in the present case.

Unenhanced MRI is the most suitable screening method for renal artery stenosis. While MRI shows a sensitivity of 85–89% and specificity of 95–96% [17,18], which is slightly lower than with contrast CT, it can easily visualize lesions and can be performed irrespective of renal function. The main drawback is that unenhanced MRI detects blood flow and magnetic resonance angiography images are reconstructed from the MRI data, so the severity of stenosis tends to be exaggerated.

While noninvasive renal artery ultrasound is often recommended for screening, it is doubtful that many physicians and sonographers can perform it properly.

MRI is widely available these days, and unenhanced MRI should be utilized for renal artery screening in patients with hypertension or cardiovascular disease.

Conclusions

Although previous large-scale clinical studies have not demonstrated the effectiveness of renal angioplasty, we treated a patient with cardiac disturbance syndrome due to renal artery occlusion in whom renal angioplasty rapidly improved the BP and endocrine abnormalities. We recommend using unenhanced MRI to screen patients with heart failure for renal artery stenosis, and revascularization by PTRA should be conducted when it is indicated from pathophysiological and anatomical perspectives.

Long-term follow-up of this patient is needed and similar cases should be collected to support this recommendation.

Conflicts of interest

None.

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