Original Paper

Percutaneous Transluminal Revascularization following an Angiotensin Receptor Blocker: Successful Treatment for Flash Pulmonary Edema and Hyponatremic Hypertensive Syndrome

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Key Words

Flash pulmonary edema · Hyponatremic hypertensive syndrome · Bilateral renal artery stenosis · Angiotensin receptor blocker · Percutaneous transluminal revascularization

Abstract

Either flash pulmonary edema or hyponatremic hypertensive syndrome has been described in renal artery stenosis. However, coexistence of these two disorders has never been previously reported. We describe a patient who presented with flash pulmonary edema and hyponatremic hypertensive syndrome associated with bilateral renal artery disease (one complete occlusion, one highly critical renal artery stenosis, the equivalent of unilateral stenosis of a solitary functioning kidney). His blood pressure, hyponatremia, and symptoms of acute heart failure were much improved by an angiotensin receptor blocker. After the procedure of percutaneous transluminal revascularization, his stenotic kidney function and serum sodium levels were completely restored.

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Introduction

Flash pulmonary edema (FPE) is a general term that is used to describe a particularly dramatic form of acute decompensated heart failure (ADHF). FPE is a well-known complication of bilateral renal artery stenosis (RAS) or unilateral stenosis of a solitary kidney [1, 2].

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Because FPE and bilateral RAS seem to be a unique entity with distinct pathophysiological, clinical, and therapeutic features, some investigators propose to name it Pickering Syndrome [1–3].

The combination of hyponatremia and renovascular hypertension is called hyponatremic hypertensive syndrome (HHS), which might also develop in a small number of patients with unilateral or bilateral RAS [4].

Herein, we report a patient with FPE and HHS due to bilateral RAS whose condition rapidly improved through treatment with an angiotensin receptor blocker (ARB), and who subsequently successfully underwent percutaneous transluminal revascularization.

Case Report

A 53-year-old man was transferred to our hospital because of accelerated deterioration of renal function. He had a 30-pack-year smoking history. Five days before admission, the patient presented at the urgent care clinic of an outside hospital complaining of headache and shortness of breath. His blood pressure (BP) was 220/130 mm Hg and coarse crackles were audible on his bilateral lower chest. Biochemical data showed impaired renal function with a serum creatinine (SCr) level of 281 $\mu\text{mol/l}$. By treatment with nifedipine (60 mg/day) and valsartan (160 mg/day), his symptoms of headache and dyspnea disappeared, and BP was well controlled rapidly. However, his renal function dramatically deteriorated to a SCr level of 524 $\mu\text{mol/l}$. Then, he was admitted to our hospital for further evaluation.

At hospitalization, his body weight was 55.0 kg, body mass index 20.8, and BP 150/90 mm Hg. His lung fields were clear on auscultation and percussion. A low-pitched systolic abdominal bruit was heard just above and to the left of the umbilicus. No peripheral edema was present. The daily urine volume was 1,300 ml.

Laboratory data showed leukocyte count was $9.35 \times 10^9/\text{l}$, hemoglobin 132 g/l, blood urea nitrogen 42.6 mmol/l, and SCr 524 $\mu\text{mol/l}$. Serum electrolyte concentrations including Na^+ (SNa), Cl^- (SCL), and K^+ (SK) were 136, 95, and 3.96 mmol/l, respectively. Plasma renin activity (PRA) and angiotensin II were increased, aldosterone was within normal range. Urinalysis showed mild proteinuria (170 mg/l). Electrocardiogram showed ST-segment depression >0.1 mV, with T-wave inversion in leads I, AVL, V5, and V6. Ultrasonography revealed kidney asymmetry, with the right kidney $6.5 \times 4.0 \times 3.5$ cm³ and the left kidney $10.8 \times 5.7 \times 5.0$ cm³. The echocardiography evaluation showed a mild concentric left ventricular (LV) hypertrophy with normal systolic function (ejection fraction 58%).

The abovementioned findings, such as atrophy of the right kidney and the rapid deterioration of renal function, when challenged by an ARB indicated ischemic nephropathy. Valsartan was discontinued because of its contraindication of renal impairment on the first hospital day. After the withdrawal of valsartan, the patient presented a gradually aggravating dyspnea and polydipsia. On the third hospital day, his BP was again elevated to $>200/110$ mm Hg, and renal function returned to pretreatment levels. Continuous intravenous pumping of sodium nitroprusside was started; however, his BP was still uncontrolled. On hospital days 7–10, his SNa decreased to 121 mmol/l, SCL to 87 mmol/l, and SK to 3.56 mmol/l; the concentration of Na^+ in the urine was 89 mmol/l (fig. 1) and of K^+ 20 mmol/l. Fractional excretion of sodium was 4.8%, and fractional excretion of potassium 30% (table 1). At that time, PRA, aldosterone, antidiuretic hormone (ADH), and B-type natriuretic peptide (BNP) were all increased (table 2). Urine osmolality was hypertonic with a daily output of approximately 1,700 ml. On the 12th hospital day, he developed severe pulmonary edema and was coughing up pink, foamy mucus. Doppler echocardiography exhibited regional wall motion abnormalities with a mildly reduced ejection fraction of 46%. Valsartan was cautiously added again in view of its good therapeutic response before admission. However, diuretics were not used due to a potential danger of exacerbation of hyponatremia. After restarting oral administration of valsartan (initial dose: 80 mg/day, maintenance: 160 mg/day), the patient's symptoms of pulmonary edema rapidly improved, and BP was normalized within 2 days. On hospital days 17–19, his SNa increased to 132 mmol/l (fig. 1), SCL to 101 mmol/l, and SK to 3.92 mmol/l. The concentration of Na^+ in the urine decreased to 20 mmol/l and K^+ to 7 mmol/l; however, his urine volume was reduced by about 30% (table 1). Both ADH and BNP had decreased to normal values, while PRA and angiotensin II were still elevated (table 2). However, his renal function deteriorated again (SCr 550 $\mu\text{mol/l}$). After 24 days of hospitalization, the patient accepted percutaneous transluminal renal artery angioplasty, which demon-

Fig. 1. Serum Na concentration in the course of hospitalization. PTRA = Percutaneous transluminal revascularization.

Table 1. Blood and urine electrolytes values

Variable	3 days before valsartan	7 days after valsartan	5 days after PTRA
SNa, mmol/l	121	132	140
SK, mmol/l	3.56	3.92	5.18
SCl, mmol/l	87	101	106
SCr, μ mol/l	285	550	150
Urine Na, mmol/l	82	20	35
Urine K, mmol/l	20	7	13
FENa, %	4.8	1.2	1.3
FEK, %	30	16	11
Serum osmolarity, mOsm/kg	256	278	283
Urine osmolarity, mOsm/kg	720	143	294
Daily urine volume, ml	1,700	1,100	2,000
Body weight, kg	55.5	57	54.5

FENa = Fractional excretion of sodium; FEK = fractional excretion of potassium; PTRA = percutaneous transluminal revascularization.

strated a proximal critical stenosis of the left renal artery (blood can only flow through the stenotic region in the systole phase) and total occlusion of the right renal artery. A balloon-expandable stent was successfully implanted into the left renal artery (fig. 2). After the procedure of renal revascularization, his urinary production increased temporarily and then tended towards normal production, his SCr level decreased to 154 μ mol/l and SNa was further elevated to 140 mmol/l within several days (fig. 1; table 1, 2). In addition, his BP was stabilized at around 135/85 mm Hg without any antihypertensive drug use. Thereafter, the patient was discharged and follow-up was arranged for him. Up to now (2 years later), his renal function remains stable with a SCr level of 100 μ mol/l, and his BP is kept within normal limits.

Discussion

FPE is a well-recognized disease, which is generally related with bilateral RAS. Sodium and water retention is one of the most important causes of ADHF. However, valsartan, an ARB, produced a rapid alleviation of the emergent condition in our patient, although his

Fig. 2. Renal artery angiography. **a** Left main renal artery pre-revascularization, **b** post-angioplasty/stent insertion of left renal artery.

Table 2. Endocrinology tests

Variable	3 days before valsartan	7 days after valsartan	5 days after PTRA	Normal range
PRA, ng·ml ⁻¹ ·h ⁻¹ *	>20	>20	0.9	0.1–2.9
Aldosterone, pg/ml*	890	195	88	29–161
Angiotensin II, pg/ml*	330	360	27	15–36
ADH, pg/ml	15.6	1.7	1.0	0.3–3.5
BNP, pg/ml	722	89.8	46.5	0.0–100

PTRA = Percutaneous transluminal revascularization. * Supine position.

kidney function deteriorated promptly accompanied by a moderately decreased urine volume and exacerbated volume expansion compared to before valsartan administration. This implied that angiotensin II (or renin-angiotensin system) might play a more important role in the development of ADHF in this patient. Except for salt and water retention, angiotensin II leads to stimulation of the sympathetic nervous system and vasoconstriction, resulting in a marked increase in BP and LV wall stress. Electrocardiogram confirmed his preexisting ischemic heart disease. A suddenly increased myocardial oxygen demand might, therefore, produce a large area of reversibly ischemic myocardium, causing transient LV dysfunction (demonstrated by the finding of regional wall motion abnormalities), raised LV end diastolic pressure, and acute pulmonary edema (or FPE). On the other hand, LV hypertrophy is among the vital reasons for LV end diastolic pressure and FPE in this patient. In addition, pulmonary capillary stress failure, caused by angiotensin II and other neurohumoral mediators, is an important pathogenetic mechanism of FPE.

FPE can be divided into two distinct phases according to the therapeutic approaches, an acute phase and a stable phase [1]. The acute phase is characterized by the occurrence of FPE which represents a hypertensive emergency requiring immediate therapeutic intervention. In the stable phase, the patient is out of FPE and has been stabilized, and renal revascularization is the treatment of choice. In the acute phase, there is no ironclad evidence so far to ex-

actly guide us on how to optimally deal with these patients. Renin-angiotensin inhibitors are contraindicated because of the risk of acute renal failure; however, these agents may offer an effective therapy when traditional drugs do not work as can be seen in this patient. Moreover, renal function always returned promptly to pretreatment levels on withdrawal of these agents [5]. For these reasons, we consider that a trial of a renin-angiotensin inhibitor is still the treatment of choice in the acute phase of FPE, and is not only confined to circumstances where revascularization is contraindicated or unsuccessful [6].

HHS has been reported infrequently. In China, HHS has never been reported up to now. However, the investigation of Agarwal et al. [4] suggests that HHS is not rare but is under-recognized. HHS is more frequently reported in patients with unilateral RAS. In patients with unilateral RAS corresponding to the 2-kidney-1-clip hypertension model [7], sustained renin secretion of the stenotic kidney with low perfusion and pressure natriuresis of the contralateral kidney are the main mechanisms to HHS development [4]. In the study by Agarwal et al. [4], HHS was also reported in association with bilateral RAS in some patients. The authors presumed that critical stenosis and intense stimulation of the renin-angiotensin system in one kidney and pressure natriuresis in the contralateral kidney with sub-severe stenosis may be underlying mechanisms [4, 8]. However, it is difficult to apply this argument to individuals with bilateral critical RAS or unilateral stenosis of a solitary functioning kidney as was seen in our patient. In some patients with one stenotic functioning kidney which may correspond to the 1-kidney-1-clip hypertension model which has been described by Tobian et al. [9], intravascular volume expansion secondary to sodium and water retention persists due to decreased perfusion to the kidney, until regulatory mechanisms establish a new equilibrium of sodium balance with more exchangeable sodium. At this equilibrium point, renal perfusion is restored with a higher BP, and renin secretion is normalized in a closing cycle [9]. Obviously, the 1-kidney-1-clip model of Tobian et al. [9] still cannot be used to explain the hyponatremia in our patient who had decreased exchangeable sodium. We suppose that various degrees of narrowing of renal arteries may result in different pathophysiological procedures. Of note, the stenosis of this patient was so severe that low renal perfusion and intense renin release might persist. Under the action of exceedingly high levels of angiotensin II, stimulation of thirst, subsequent inappropriate fluid intake [10], and the enhanced release of ADH may be the initial factors leading to hyponatremia in our patient [11]. Severe hypokalemia, which is frequently associated with RAS, may block the action of ADH; however, mild potassium depletion, as can be seen in our patient, may enhance the effect of ADH on the collecting tubules [12]. The high urinary Na^+ (inappropriate natriuresis) and concentrated urine of our patient implied the prominent action of ADH. Direct renal action of angiotensin II to retain water in excess of sodium, as well as enhanced BNP secretion in response to high BP, may also play a part. In addition, impairment in the capacity to eliminate solute-free water due to renal failure may contribute to the development of hyponatremia. Therefore, all of the abovementioned mechanisms may act together to contribute to the occurrence and development of hyponatremia. However, the augmented effect of ADH induced by the activated renin-angiotensin system may play a more important role. Accordingly, we consider that it is reasonable and appropriate to diagnose this case as HHS. Further, the fact that the abnormality of hyponatremia was corrected with an ARB adds weight to our hypothesis [13]. We presume that the mechanism of hyponatremia in this patient may be more like HHS in malignant hypertension than that in unilateral RAS.

Our case is unique in that there is a coexistence of FPE and HHS. Theoretically, it is reasonable that FPE and HHS occasionally co-present in a patient because both are associated with an excessive activation of the renin-angiotensin system and renal artery disease. The reason why HHS rarely occurs in patients with FPE may be related to early emergency treatments, such as hemodialysis, renin-angiotensin inhibitors, or diuretics, by which fluid-elec-

trolyte imbalance is restored or covered up. In our patient, it took more than 7 days for hyponatremia to evolve from mild to evident. Therefore, a sufficient observation period with no use of treatments that may disturb electrolyte balance is necessary to meet HHS with FPE.

In summary, our report demonstrates that HHS may occur in patients with high-grade bilateral RAS or unilateral stenosis of a solitary functioning kidney, even in patients with FPE. Natriuresis caused by direct or indirect action of angiotensin II and impaired renal free water clearance might be the main pathophysiological mechanisms.

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Disclosure Statement

The authors declare that no conflicts of interest exist.

References

- 1 Messerli FH, Bangalore S, Makani H, Rimoldi SF, Allemann Y, White CJ, Textor S, Sleight P: Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering Syndrome. *Eur Heart J* 2011;32:2231–2235.
- 2 Pelta A, Andersen UB, Just S, Bækgaard N: Flash pulmonary edema in patients with renal artery stenosis – the Pickering Syndrome. *Blood Press* 2010;20:15–19.
- 3 Pickering TG, Herman L, Devereux RB, Sotelo JE, James GD, Sos TA, Silane MF, Laragh J: Recurrent pulmonary oedema in hypertension due to bilateral renal artery stenosis: treatment by angioplasty or surgical revascularisation. *Lancet* 1988;2:551–552.
- 4 Agarwal M, Lynn KL, Richards AM, Nicholls MG: Hyponatremic-hypertensive syndrome with renal ischemia: an underrecognized disorder. *Hypertension* 1999;33:1020–1024.
- 5 Jackson B, Matthews PG, McGrath BP, Johnston CI: Angiotensin converting enzyme inhibition in renovascular hypertension: frequency of reversible renal failure. *Lancet* 1984;28:225–226.
- 6 Fujigaki Y, Togawa A, Miyaji T, Suzuki H, Ohashi N, Fukasawa H, Yasuda H, Yamamoto T, Hishida A, Yonemura K: Rapid improvement of acute pulmonary edema with angiotensin converting enzyme inhibitor under hemodialysis in a patient with renovascular disease. *Ther Apher Dial* 2004;8:148–152.
- 7 Galvez OG, Roberts BW, Mishkind MH, Bay WH, Ferris TF: Studies of the mechanism of contralateral polyuria after renal artery stenosis. *J Clin Invest* 1977;59:609–615.
- 8 Seracini D, Pela I, Favilli S, Bini RM: Hyponatraemic-hypertensive syndrome in a 15-month-old child with renal artery stenosis. *Pediatr Nephrol* 2006;21:1027–1030.
- 9 Tobian L, Coffee K, McCrea P: Contrasting exchangeable sodium in rats with different types of Goldblatt hypertension. *Am J Physiol* 1969;217:458–460.
- 10 Fitzsimons JT: Angiotensin, thirst, and sodium appetite. *Physiol Rev* 1998;78:583–686.
- 11 Bonjour JP, Malvin RL: Stimulation of ADH release by the renin-angiotensin system. *Am J Physiol* 1970;218:1555–1559.
- 12 Richter HS: Action of antidiuretic hormone in potassium-depleted rats; relation to aldosteronism. *Proc Soc Exp Biol Med* 1958;97:141–144.
- 13 Kwon TH, Nielsen J, Knepper MA, Frøkier J, Nielsen S: Angiotensin II AT1 receptor blockade decreases vasopressin-induced water reabsorption and AQP2 levels in NaCl-restricted rats. *Am J Physiol Renal Physiol* 2005;288:F673–F684.