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**ORIGINAL ARTICLE**

# Flash pulmonary edema in patients with renal artery stenosis – The Pickering Syndrome

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**Abstract**

*Aim.* We report the prevalence of flash pulmonary edema in patients consecutively referred for balloon angioplasty of uni- or bilateral renal artery stenosis (PTRA), and describe the characteristics of this special fraction of the patients. We further report two unusual cases. *Methods and material.* Review of medical records from 60 patients consecutively referred for uni- or bilateral PTRA from 2004–2005 in Copenhagen County. *Results.* Eight out of 60 patients had one or more episodes of flash pulmonary edema before PTRA. Compared with the remaining patients, they had a higher prevalence of bilateral stenosis (50% vs 27%) and coronary artery disease (75% vs 28%). However, only one of eight had severe systolic dysfunction of the left ventricle. After PTRA, two recurrences of flash pulmonary edema were observed. One was caused by severe restenosis and did not recur after aorto-renal bypass surgery. The other one was caused by rapid atrial fibrillation and did not recur after pacemaker and medical treatment. *Conclusion.* Flash pulmonary edema can be observed in patients with unilateral as well as bilateral stenosis. The prognosis is usually excellent upon treatment of the stenoses. Recurrences are rare unless restenosis occurs, and therefore, regular control, e.g. by Doppler-ultrasound examination is recommended.

**Key Words:** *Balloon angioplasty, pulmonary edema, renal artery obstruction, renal artery stenosis*

## Introduction

Renal artery stenosis accounts for 1–5% of all cases of hypertension. Atherosclerosis is by far the most frequent cause of renal artery stenosis (1). Stenoses can be asymptomatic, especially in elderly people (2), but in case of progressive stenosis there is a loss of function and atrophy of the kidney. The primary symptom is hypertension, which is often severe and resistant to medical treatment (3). In a number of cases, the patients develop acute episodes of pulmonary congestion, so-called "flash pulmonary edema". This symptom was first reported by the late professor Thomas G. Pickering and coworkers (4), and has now been named "The Pickering Syndrome".

In this paper, we report the frequency of this syndrome among patients referred to percutaneous transluminal renal artery angioplasty (PTRA) for renal artery stenosis in Copenhagen County over a 2-year period. We compare the studies published so far, and present two unusual cases.

## Materials and methods

The study is based on a retrospective review of medical records of all patients with renal artery stenosis referred for PTRA at the Department of Radiology, Gentofte Hospital, between February 2004 and December 2005. The patients were referred from the medical departments in Copenhagen County and the provincial hospitals of Sealand, representing an approximate uptake area of 2 million people.

The medical records of all patients were reviewed. The following information was obtained: history of pulmonary edema, diabetes mellitus, atherosclerotic heart disease, peripheral vascular disease, smoking, and, when available, an estimate of left ventricular function as assessed by echocardiography. EF ≥55% was considered normal left ventricular function (5).

Our usual procedure for patients with renal artery stenosis is as follows: unless acute, the decision of referral is made on a specialist conference with a

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vascular surgeon, and specialists in interventional radiology, hypertension, clinical physiology and nephrology, and is based on clinical evidence and laboratory investigations (24-h blood pressure measurement, captopril renography with clearance estimate, Doppler-ultrasound (US) examination of renal arteries and other examinations as necessary). After PTRA, all patients are followed regularly with renography and Doppler-US.

All interventions in the study period were made by the same experienced radiologist, during the diagnostic renal angiography. A hemodynamically significant stenosis was defined as being greater than 70% of luminal diameter by visual inspection, or by having a systolic pressure gradient over the stenosis of at least 20 mmHg (6,7). The intervention was PTRA and stent placement unless technically unfeasible. Selective angiography was performed after stent placement, to assure correct localization.

The study was conducted in accordance with the Helsinki II declaration.

## Results

We included 37 men and 23 women in the study. Please refer to Table I for clinical characteristics. Fibromuscular dysplasia was the cause of renal artery stenosis in five patients (8%). The remaining 55 patients (92%) had atherosclerotic disease, including all patients with flash pulmonary edema.

The reason for referral to invasive treatment was renovascular hypertension in 36 cases, improvement or preservation of renal function in one case, or both in 16 patients. Eight patients were referred because of one or more episodes of flash pulmonary edema; 75% had more than one episode.

All except one patient underwent PTRA. Bilateral stenosis was present in 16 (27%), and 10 of these patients underwent bilateral PTRA, whereas six underwent unilateral PTRA. Nine (15%) patients had unilateral stenosis in a solitary functioning kidney. One patient had recurrent restenosis, and underwent re-PTRA and subsequently an aorto-renal bypass operation.

Mean follow-up time was 15 months, with a range of 3–40 months. In patients with a history of pulmonary edema, mean follow-up time was 16.4 months, with a range of 3–27 months. During the follow-up period, two patients died and two were lost to follow-up.

An estimate of left ventricular function was available in all patients with a history of pulmonary edema. One patient had severe left ventricular dysfunction with left ventricular ejection fraction (EF) 30%, while five had a mild dysfunction (EF 40–50%). Five patients had hypertrophy of the left ventricle. In patients without episodes of pulmonary edema, only 18 had an echocardiography. In five (27%), EF was abnormal.

Coronary artery disease was present almost three times more often in patients with pulmonary edema.

Diabetes, cerebral insults and peripheral vascular disease tended to occur more frequently in patients experiencing flash pulmonary edema, but the differences were not significant.

Recurrence of pulmonary edema after PTRA was observed twice. One patient had recurrent restenosis (see case report 2), and had no further episodes of pulmonary congestion after successful treatment. In another patient, the pulmonary congestion was caused by rapid atrial fibrillation. This patient received a pacemaker implantation, and did not experience any further episodes.

Table I. Clinical characteristics of 60 patients with symptomatic renal artery stenosis.

| | Pulmonary edema ($n = 8$) | No pulmonary edema ($n = 52$) |
|---|---|---|
| Mean age (years) | 69 | 58 |
| Male/female | 4/4 | 34/18 |
| Unilateral stenosis | 4 (50%) | 32 (61%) |
| Bilateral stenosis[a] | 4 (50%) | 20 (38%) |
| Mean systolic blood pressure ± SD (mmHg) | 174 ± 22 | 164 ± 26 |
| Mean diastolic blood pressure ± SD (mmHg) | 86 ± 24 | 91 ± 13 |
| No. of antihypertensive drugs | 3.3 | 2.9 |
| Mean plasma creatinin ± SD (μmol/l) | 157 ± 75 | 149 ± 74 |
| Cerebral insult | 4 (50%) | 13 (25%) |
| Coronary artery disease | 6 (75%)[b] | 15 (28%)[b] |
| Peripheral vascular disease | 5 (62%) | 15 (28%) |
| Reduced EF <50% | 6 (75%) | (28%)[c] |
| Diabetes mellitus | 3 (38%) | 11 (21%) |
| Hypercholesterolemia | 7 (85%) | 43 (89%) |
| Smokers or former smokers | 8 (100%) | 41 (79%) |

[a]Or one kidney with a stenosis.
[b]$p<0.05$ by chi-square test.
[c]EF only assessed in 18 subjects.

## Case reports

*Case report 1*

A 65-year-old man with hypertension for 7 years. Ischemic heart disease, but with left ventricular EF more than 50%. Peripheral artery disease with intermittent claudication. He was hospitalized with flash pulmonary edema and severe hypertension, and treated in the intensive care unit with infusions of furosemide, nitroglycerine and continuous positive airway pressure (CPAP). Doppler-US examination subsequently revealed bilateral renal artery stenosis, and the patient was treated with bilateral PTRA. At the end of the invasive procedure, the patient developed severe respiratory distress and was transferred immediately to the intensive care unit, where flash pulmonary edema was diagnosed. The condition was stabilized within 24 h. After

bilateral PTRA, there has been no recurrence of pulmonary edema.

*Case report 2*

A 56-year-old man, smoker, with diabetes mellitus type 2, angina pectoris, peripheral artery disease and a former cerebral insult. He was admitted with uncontrollable hypertension, and bilateral renal artery stenosis was diagnosed by Doppler-US examination. EF at admission was 40–45%. A bilateral PTRA with stent placement was successfully performed (Figure 1). Shortly after the PTRA, the patient had strong abdominal pain. An acute computerized tomography (CT) scan showed rupture of the right kidney (Figure 2), necessitating an acute nephrectomy. Six months later the patient developed flash pulmonary edema and severe renal insufficiency. Doppler US showed severe restenosis of the left renal artery. PTRA with stent-in-stent placement was performed, and the renal function was normalized. Six weeks later flash pulmonary edema and renal failure recurred because of severe restenosis, and an aorto-renal bypass operation was successfully performed. In the following 3 years, there have been no further episodes of pulmonary edema, and renal function is within normal limits.

## Discussion

Flash pulmonary edema is a violent and life threatening symptom, causing severe dyspnea and anxiety in the patient.

We report the prevalence and the effect of invasive treatment on this symptom in patients referred to PTRA for renal artery stenosis in Copenhagen County. We also present two unusual cases.

Flash pulmonary edema occurred in 14%. Compared with patients with renal artery stenosis, but without this symptom, the group with flash pulmonary edema was characterized by having a higher rate of coronary artery disease and reduced left ventricular EF. In contrast to other studies, only half of our patients had bilateral stenosis. The cure rate for flash pulmonary edema among our patients was as high as seven of eight patients with patent renal arteries after treatment.

Four other studies have reported on the prevalence and treatment effect of flash pulmonary edema (4,8–10) (Table II). Pickering et al. (4) were the first to describe the relation between renovascular hypertension and flash pulmonary edema. They observed that pulmonary edema was more likely to occur in patients with bilateral renal artery stenosis or unilateral stenosis in a solitary functioning kidney. They also noted that coronary artery disease occurred

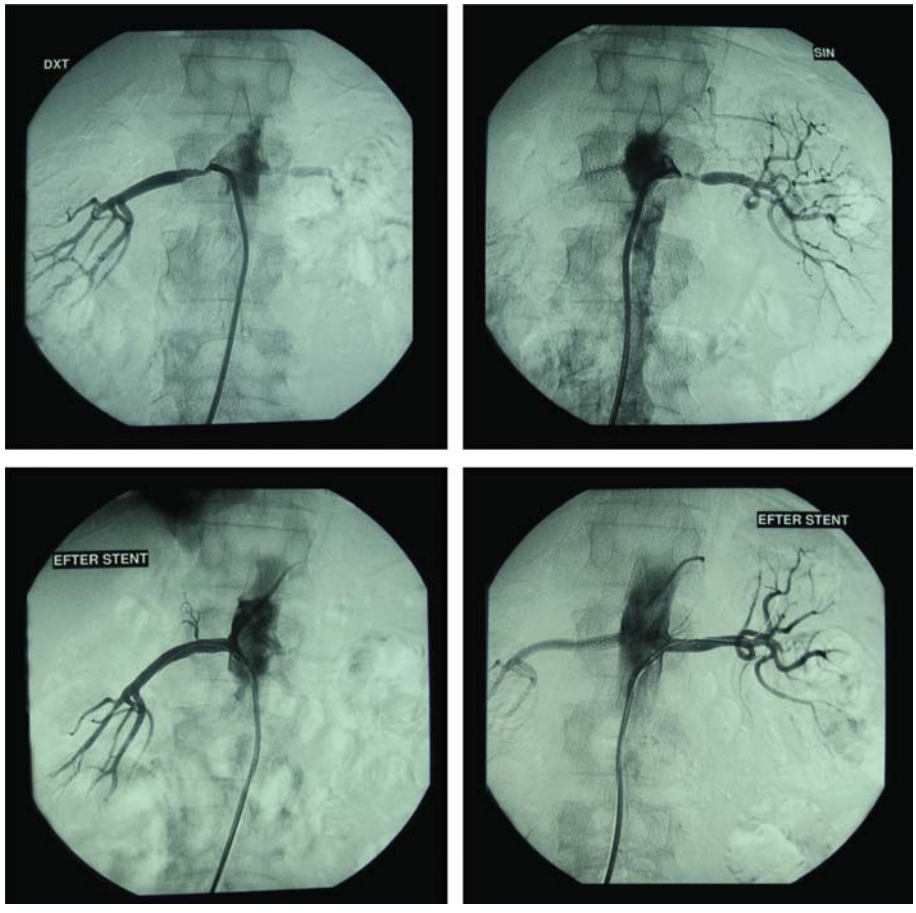


Figure 1. Renal angiogram showing bilateral renal artery stenoses before percutaneous transluminal renal artery angioplasty (PTRA) (top) and patent renal arteries after PTRA (bottom).

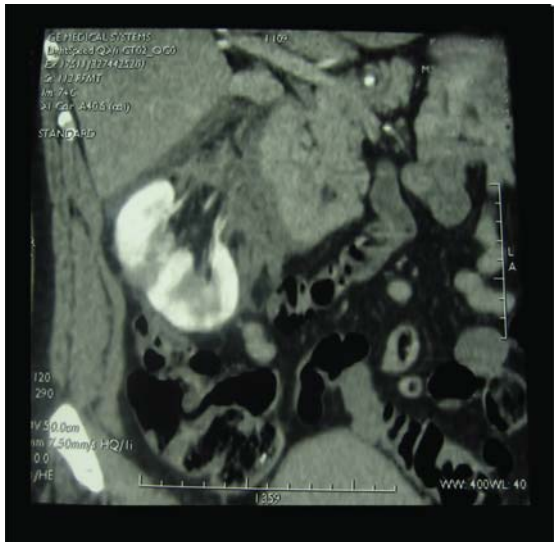

Figure 2. Computerized tomography scan showing rupture of the kidney after percutaneous transluminal renal artery angioplasty.

more frequently in renal artery stenosis patients with episodes of pulmonary edema.

The fraction of patients with renal artery stenosis that has pulmonary edema is very variable in the studies, ranging from 10% to 30%. The reason for this is not clear, but may reflect different referral patterns from e.g. cardiologists and nephrologists, or different awareness of this particular pathophysiological relationship. The extremely variable fraction of patients having bilateral affection, ranging from 50% in our study to 100%, also suggests that differences in the referral patterns exist.

Recurrence rates in the studies ranged from 6% to 23%. It is important to discriminate between recurrence of pulmonary edema in a successfully treated patient (which implies that the symptom was probably not caused by renal artery stenosis) and recurrence because of restenosis (meaning that the cause of the symptom is still present). In the study with the highest recurrence rate (10), restenosis was the major cause. In the study by Gray et al. (11), however, the recurrence rate was 18% despite a systematic retreatment for restenosis. An analysis of the reasons for recurrencies in this study is not provided, but the study underlines the multifactorial nature of recurrent pulmonary edema.

The pathophysiology of recurrent pulmonary edema is complex, and has recently been subject to an excellent review (12). Obviously, retention of salt and water because of excretion failure caused by severe parenchymal renal disease or bilateral renovascular affection can cause pulmonary edema, as is well known from dialysis patients. Severe systolic left ventricular dysfunction is also an obvious and well known cause. However, in unilateral renal artery stenosis, the sodium retention caused by the high renin/aldosterone levels should be offset by the contralateral kidney, and it is less clear why pulmonary edema should occur. Conn's syndrome, by comparison, is characterized by high blood pressure and severe sodium retention related to high aldosterone levels, but pulmonary congestion is rarely observed. It must be anticipated that other factors contribute when pulmonary edema occurs in patients with unilateral renovascular disease, such as systolic and diastolic heart failure.

Only one study has reported the prevalence of renal artery stenosis in patients with flash pulmonary edema (13). The authors found that renal artery stenosis was present in 48% of subjects hospitalized with flash pulmonary edema, which underlines the central role of renal artery stenosis in the pathogenesis of this symptom.

In case report 1, we believe the most likely explanation for the postprocedural episode of flash pulmonary edema was bilateral renal artery spasm, which is a rare complication to PTRA. A case of flash pulmonary edema related to renal artery spasm has been reported (14). If this happens during the procedure, it can be treated by infusion of nitroglycerine into the renal artery, but in this case the catheters had been retracted and pulmonary congestion ensued. Eventually the spasms resolved and no further episodes of pulmonary congestion were observed in this patient.

Case report 2 illustrates another rare complication to PTRA, namely spontaneous rupture of the kidney after successful reperfusion. We have not been able to find another report of this complication in the literature. Furthermore, this patient suffered from repeated restenosis of the remaining renal artery with short intervals. Each time, the patient was hospitalized with severe renal insufficiency and pulmonary congestion. The problem resolved after aorto-renal bypass operation.

Table II. Studies reporting the prevalence of flash pulmonary edema in subjects with uni- or bilateral renal artery stenosis (RAS).

| | | Flash pulmonary edema | | No flash pulmonary edema | |
|---|---|---|---|---|---|
| | Subjects | Unilateral RAS | Bilateral RAS | Unilateral RAS | Bilateral RAS |
| This study | 60 | 4 | 4 | 32 | 20 |
| Pickering et al. (4) | 55 | 1 | 12 | 13 | 24 |
| Messina et al. (9) | 191 | 1 | 16 | | |
| Bloch et al. (10) | 90 | 4 | 23 | 30 | 33 |
| Gray et al. (11) | 207 | 0 | 39 | – | – |

## Conclusion

Flash pulmonary edema in patients with renal artery stenosis can be observed in unilateral as well as bilateral stenosis. Even though it seems often to be multifactorial, the prognosis is usually excellent upon treatment of the stenoses. Recurrence is rare unless restenosis occurs, and therefore, regular control, e.g. by Doppler-US, is recommended.

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