



## FREQUENCY OF RENAL ARTERY STENOSIS IN HYPERTENSIVE PATIENTS PRESENTING WITH FLASH PULMONARY EDEMA

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### ABSTRACT

**BACKGROUND:** Flash pulmonary edema is an acute decompensated heart failure and dramatic symptoms of pulmonary edema. It is one of the neglected cause of pulmonary edema. Since the initial observation, many researchers have shown interest in this clinical entity. Non-invasive imaging of renal vessels may be acquired by CT angiography. CT renal angiography is by far statistically correct and thereby, invasive procedure is no longer required.

**OBJECTIVE:** To determine the frequency of bilateral stenosis of renal arteries in hypertensive patients admitted with flash pulmonary edema with preserved LV function.

**MATERIAL AND METHODS:** This was a descriptive observational study carried out at Cardiology Department, Punjab Institute of Cardiology, Lahore over a period of 6 months. 150 patients admitted with flash pulmonary edema were included in this study through non-probability, purposive sampling technique. Patients were scheduled for CT renal angiogram. Thin section 64 multi-slice CT renal angiogram was acquired and the presence or absence of  $\geq 70\%$  stenosis in renal arteries was evaluated.

**RESULTS:** The mean age of patients was  $35.4 \pm 11.9$  years. There were 112 (75%) males while 38 (25%) were females. Dyspnea was present in all (100%) patients. According NYHA class, 1 (0.67%) had class II-III, 95 (63.3%) had class III, 12 (8%) fall in class III-IV while 42 (28%) in class IV. Chest pain was present in 15 (10%) cases. Bilateral stenosis of renal arteries was present in 58 (38.7%) subjects. Left renal arterial stenosis was present in 61 (40.7%) cases. Right renal arterial stenosis was detected in 59 (39.3%) subjects.

**CONCLUSION:** The patients admitted with the diagnosis of sudden acute or flash pulmonary edema should be evaluated for the presence of renal artery stenosis especially bilateral stenosis.

**KEY WORDS:** Bilateral stenosis of renal arteries, hypertension, pulmonary edema, left ventricular function

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## INTRODUCTION

**F**lash pulmonary edema is an acute decompensated heart failure and dramatic symptoms of pulmonary edema. In 1988, Pickering et al while investigating the etiology reported its association with stenotic renal artery and afterwards it was labeled as Pickering Syndrome.<sup>1</sup> Up till now 29 case reports, 9 cases and 10 clinical evaluations of pulmonary edema (flash) and renal artery stenosis is published but only a few studies showed the existence of renal artery stenosis.<sup>2</sup> Since the initial observation, many researchers had shown interest in this clinical entity not only because of availability of modern diagnostic modalities required to diagnose this condition but also for two reasons. Firstly, effective renal artery revascularization can dramatically eliminate the life threatening paroxysms of pulmonary edema that necessitate repeated hospital admissions. Secondly, angiotensin converting enzyme (ACE) inhibitors may be used to treat these patients.<sup>3</sup>

Many reports explain atherosclerotic changes in renal vessels during routine angiography of coronary arteries.<sup>4,5</sup> Pickering initially published data of 11 patients with hypertension and who had renal artery stenosis of both sides. The patients presented with flash pulmonary edema and then extended this series to 90 patients. This study concluded that pulmonary edema is reduced in single artery stenosis then bilateral, and more importantly most of the patients were relieved from deadly episodes of pulmonary edema with successful revascularization of renal arteries.<sup>6</sup> Bilateral renal artery stenosis refers to edema of pulmonary vasculature by three mechanisms: ineffective natriuresis, hemodynamic overload and augmented diastolic dysfunction along with pulmonary vasculature gas barrier failure. Sympathetic drive is activated followed by decrease in perfusion of renal vasculature through activation of renin angiotensin system activation.<sup>7-10</sup>

LVEF during flash pulmonary edema and disappearance of symptoms are found to be similar.<sup>11</sup> Renal artery stenosis is a cause of repeated presentation of sudden edema in hypertensive patients.<sup>12</sup> Frequent association has been observed between LV diastolic dysfunction with exacerbation of flash pulmonary edema.<sup>13</sup> Those with preserved as well as compromised ventricular function, assessment of renal profile and function is leading prognostic outcome.<sup>14</sup> Although LVEF is an indicator of LV dysfunction, it does not have a strong relationship with clinical symptoms of heart failure.<sup>14</sup> Persistent

hypertension despite several medications, recurrent pulmonary edema episodes in the absence of or out of proportion to LV dysfunction warrants the presence of renal artery stenosis.<sup>15</sup>

Persistent recurring pulmonary edema symptoms deserve intervention.<sup>16</sup> Non-invasive imaging of renal vessels may be acquired by CT angiography. CT angiography provides extra images of aorta, 3D visualization. CT angiography of renal arteries has specificity and sensitivity of 83% and 92% respectively.<sup>17</sup> Multi-slice CT enhances spatial and temporal images.<sup>18</sup> CT renal angiography is by far statistically absolutely correct that means invasive procedure is no longer required.<sup>19,20</sup>

Our study aims at determination of renal artery stenosis in hypertensive patients admitted with acute pulmonary edema. The results of study will enable us to recommend guidelines for screening these patients with this potentially treatable cause of pulmonary edema through revascularization of the renal arteries rather than just ameliorating the symptoms in emergency departments. Consequently, these patients will not require repeated hospital admissions thus reducing utilization of health resources.

## MATERIAL AND METHODS:

This was a descriptive observational study carried out at Cardiology Department, Punjab Institute of Cardiology, Lahore over a period of 6 months in the year 2017. 150 patients admitted with flash pulmonary edema were included in this study through non-probability, purposive sampling technique. The sample size was calculated by taking 48.3% frequency of stenosis of renal arteries in patients with flash pulmonary edema<sup>21</sup>, 8% absolute precision and confidence level of 95%. Patients with new onset or previous hypertension with pulmonary edema, acute onset of symptoms during a period of less than 24 hours, chest radiograph consistent with findings of acute pulmonary edema and preserved LV function (LVEF > 50%) were included after the consent. Patients with history of ischemic heart disease, myocardial infarction and CABG, patients with raised cardiac bio-markers like Troponin-T at presentation, iatrogenic fluid overload, evidence of arrhythmia e.g., atrial fibrillation on ECG, patients with history of valvular or congenital heart disease, normal serum level of B-type natriuretic peptide (BNP) and contraindications to undergo CT angiography, like cardiac arrhythmias, renal failure, contrast nephropathy, renal transplant and allergy to contrast medium were excluded.

Patients' characteristics and clinical data were

recorded. The patients presenting in emergency department with pulmonary edema were classified according to NYHA classification. These patients underwent ECG together with blood sampling for cardiac biomarkers, CK-MB [reference value: < 24 U/L], cardiac troponins [reference value: < 100 pg/L], renal panel & BNP [< 100 pg/ml]. Chest radiograph was taken. Patients underwent elective echocardiography within one week of presentation by a single operator and CT renal angiogram was done. Thin section 64 multi-slice CT was acquired. Images were transferred to a workstation for evaluation. The presence or absence of  $\geq 70\%$  stenosis at any site along the course of renal arteries was noticed. All statistical analysis was done with version 20 of SPSS. Variables (quantitative) like age, expressed as mean + standard deviation. Variables (qualitative) like gender, symptoms, cardiac markers and CT renal angiography findings were presented as frequencies.

**RESULTS:**

The mean age of patients was  $35.4 \pm 11.9$  years. There were 112 (75%) males while 38 (25%) females. Dyspnea was present in all (100%) patients. According NYHA class, 1 (0.67%) had class II-III, 95 (63.3%) had class III, 12 (8%) fall in class III-IV while 42 (28%) fall in class IV. Chest pain was present in 15 (10%) cases. Table 1

Involvement of both renal arteries with significant stenosis was detected in 58 (38.7%) subjects. Out of them, 25 (16.7%) had severe stenosis, 16 (10.8%) had moderate stenosis, 17 (11.3%)

**Table 1: Patients baseline characteristics**

n	150
Age (years)	35.4±11.9
Male	112 (75%)
Female	38 (25%)
NYHA class	
II-III	1 (0.67%)
III	95 (63.3%)
III-IV	12 (8%)
IV	42 (28%)
Chest pain	15 (10%)
Troponin T positive	15 (10%)

**Table 2: Anatomical side and severity of renal artery stenosis**

Renal Artery Stenosis	Total / Severity	Frequency(%)
Bilateral	Total	58 (38.7%)
	Severe	25 (16.7%)
	Moderate	16 (10.8%)
	Mild	17 (11.3%)
	Normal	92 (61.3%)
Left	Total	61 (40.7%)
	Severe	31 (20.7%)
	Moderate	20 (13.3%)
	Mild	10 (6.7%)
	Normal	89 (59.3%)
Right	Total	59 (39.3%)
	Severe	28 (18.7%)
	Moderate	13 (8.7%)
	Mild	18 (12.0%)
	Normal	91 (66.7%)

had mild stenosis while 92 (61.3%) did not have stenosis in bilateral side. Stenosis of left renal artery stenosis was noticed in 61 (40.7%) subjects. Out of them, 31 (20.7%) had severe stenosis, 20 (13.3%) had moderate stenosis, 10 (6.7%) had mild stenosis while 89 (59.3%) did not have stenosis in left side. Stenosis of right renal artery was present in 59 (39.3%) subjects. Out of them, 28 (18.7%) had severe stenosis, 13 (8.7%) had moderate stenosis, 18 (12.0%) had mild stenosis while 91 (66.7%) did not have stenosis in right side. Table 2

**DISCUSSION:**

Our results showed that number of male hypertensive patients with stenosis of renal artery presented with pulmonary edema were higher than females indicating that males are at increased risk of RAS with flash pulmonary edema (75% vs. 25%). Oana RD et al established that RAS with flash pulmonary edema is more frequent in male patients as compared to female patients (60% vs. 40%), the contradiction may be because of selection bias of female patient.<sup>22</sup> Sharifkazemi MB et al established that RAS with flash pulmonary edema is more frequent in female subjects as compared with male patients (66% vs. 33%).<sup>21</sup> The present study provides evidence that the mean age of the RAS with flash pulmonary edema patient was  $37.8 \pm 12.29$  years. Oana RD et al reported that age of the RAS with flash pulmonary edema patient was  $58.85 \pm 15.7$  years.<sup>22</sup> Alhaddad AL et al et al found that age of the RAS with flash pulmonary edema patient was  $68 \pm 0.2$  years.<sup>23</sup> Sharifkazemi MB et al reported that age of the RAS with flash pulmonary edema patient was  $60 \pm 10.6$  years.<sup>21</sup> In contrast to these studies present study showed dissimilar result may be due to small sample size.



All patients in our study presented with the complaint of dyspnea. Oana RD et al demonstrated that prevalence of dyspnea was in 88% hypertensive patients with flash pulmonary edema.<sup>22</sup> Sharifkazemi MB et al examined that the prevalence of dyspnea was 91%.<sup>21</sup> Alhaddad AL et al reported low prevalence of dyspnea patients with flash pulmonary edema presenting with elevated blood pressure upto 58%.<sup>23</sup> The present study demonstrated that the NYHA class III was present in 63.3% hypertensive patients with flash pulmonary edema. Oana RD et al found that NYHA class III was present in 56.3% hypertensive patients with flash pulmonary edema.<sup>22</sup> Sharifkazemi MB et al examined that the NYHA class III was noticed in 48% hypertensive patients with flash edema.<sup>21</sup> Alhaddad AL et al reported NYHA class III was reported in 47% hypertensive patients with flash pulmonary edema.<sup>23</sup>

Alhaddad AL et al reported that chest pain was found to be as less as 16% in hypertensive patients with flash pulmonary edema.<sup>23</sup> Oana RD et al scrutinized that chest pain was present in 14% patients of hypertension with flash pulmonary edema.<sup>22</sup> Further study by Sharifkazemi MB et al examined that patients having chest pain presenting with hypertension with flash pulmonary edema was 12%.<sup>21</sup> Messerli et al established that chest pain was as higher as 20% in hypertensive patients with flash pulmonary edema.<sup>2</sup> However, improvement in medicine in this study might have led to improvement in chest pain, present study reported only 10% patients presenting with chest pain.<sup>24</sup>

Messerli et al., examined the prevalence rate of bilateral RAS to be 4% to 40% out of all patients with RAS<sup>2</sup>, while according to the Rimoldi et al results showed the prevalence of bilateral RAS was 25% in cases of RAS.<sup>25</sup> Ghaffari et al found the prevalence of bilateral RAS was identified in 42.5% cases.<sup>26</sup> Present study reported that severity of stenosis of both renal arteries was present in higher number of patients i.e 25%. Previous study by Alhaddad IA, et al reported severity of the bilateral renal artery stenosis in 5.8%.

Present study reported high frequency of the bilateral stenosis of renal arteries in patients with hypertension was 33%, in contrast to previous literature by Leandri et al (2004) examined that the prevalence of bilateral stenosis of renal ar-

teries was as high as 31%.<sup>27</sup> Alhaddad et al (2001) reported that the prevalence of bilateral RAS was as high as 38.5%.<sup>23</sup> Aqel et al (2003) established similar results and reported high prevalence of the bilateral stenosis of renal arteries in hypertensive subjects.<sup>28</sup> Ghaffari et al (2009) scrutinized that bilateral stenosis of renal arteries in hypertensive patients was found to be as higher as 42.5%.<sup>26</sup> Messerli et al established that bilateral stenosis of renal arteries was present in 20% hypertensive subjects.<sup>2</sup>

Present study reported that 28/59 patients had severe right RAS, 13/59 had moderate right RAS and 18/59 had mild right RAS, only 31/61 patients had severe left RAS, 20/61 had moderate left RAS and 10/61 had mild left RAS. Sharifkazemi MB et al reported that 0/23 patients had severe right RAS, 6/23 had moderate right RAS and 6/23 had mild right RAS, only 1/37 patients had severe left RAS, 22/37 had moderate left RAS and 11/37 had mild left RAS.<sup>21</sup> Bilateral stenosis of renal arteries was also high in our study.

McMahon CJ et al established that high frequency of bilateral stenosis of renal arteries in hypertensive patients was upto 30%, present study reported similar results.<sup>3</sup> According to the Anna Pelta et al higher prevalence of bilateral stenosis of renal arteries in hypertensive patients was upto 50%.<sup>29</sup> Further study by Bloch et al also reported high frequency of bilateral stenosis of renal arteries in hypertensive patients presenting with flash pulmonary edema upto 41%.<sup>30</sup> Oana RD et al scrutinized a lower prevalence of bilateral stenosis of renal arteries i.e 20%, due to small sample size. Oana RD study showed dissimilar results.<sup>22</sup> As the severe cases of the renal artery stenosis (70–99% in both renal arteries) are detected in 94/150 patients (62.67%) due to that present study showed dissimilar result in contrast with these studies.

The main limitation of the study was small sample volume and study was carried out in a single centre, so the future studies should be carried out with a large sample size and in multiple centers to improve the power of study.

#### **CONCLUSION:**

The patients admitted with the diagnosis of sudden acute or flash pulmonary edema should be evaluated for the presence of renal artery stenosis especially bilateral stenosis.



## REFERENCES

1. Pickering T, Devereux R, James G, Silane M, Herman L, Sotelo J, et al. Recurrent pulmonary oedema in hypertension due to bilateral renal artery stenosis: treatment by angioplasty or surgical revascularisation. *The Lancet* 1988;332(8610):551-2.
2. Messerli FH, Bangalore S, Makani H, Rimoldi SF, Allemann Y, White CJ, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering syndrome. *European heart journal* 2011;32(18):2231-5.
3. McMahon CJ, Hennessy M, Boyle G, Feely J, Meaney JF. Prevalence of renal artery stenosis in flash pulmonary oedema: Determination using gadolinium-enhanced MRA. *European journal of internal medicine* 2010;21(5):424-8.
4. Yang S-N, Sun S-S, Zhang G, Chou K-T, Lo S-W, Chiou Y-R, et al. Left ventricular ejection fraction estimation using mutual information on technetium-99m multiple-gated SPECT scans. *Biomedical engineering online* 2015;14(1):119.
5. Harding MB, Smith LR, Himmelstein SI, Harrison K, Phillips HR, Schwab SJ, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. *Journal of the American Society of Nephrology* 1992;2(11):1608-16.
6. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *American journal of hypertension* 1999;12(1):01-7.
7. Murphy TP, Rundback JH, Cooper C, Kiernan MS. Chronic renal ischemia: implications for cardiovascular disease risk. *Journal of vascular and interventional radiology* 2002;13(12):1187-98.
8. Rundback JH, Gray RJ, Rozenblit G, Poplasky MR, Babu S, Shah P, et al. Renal artery stent placement for the management of ischemic nephropathy. *Journal of vascular and interventional radiology* 1998;9(3):413-20.
9. RITZ KA, DANILO FLISER, EBERHARD. The sympathetic nervous system and the kidney: its importance in renal diseases. *Blood pressure* 1998;7(sup3):14-9.
10. Grisk O, Rettig R. Interactions between the sympathetic nervous system and the kidneys in arterial hypertension. *Cardiovascular research* 2004;61(2):238-46.
11. Gandhi SK, Powers JC, Nomeir A-M, Fowle K, Kitzman DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *New England Journal of Medicine* 2001;344(1):17-22.
12. Missouri C, Belli A, MacGregor G. "Apparent" heart failure: a syndrome caused by renal artery stenoses. *Heart* 2000;83(2):152-5.
13. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrology Dialysis Transplantation* 2009;25(3):813-20.
14. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113(5):671-8.
15. Kumar S. Bilateral renal artery stenosis presenting as flash pulmonary edema. *Japi* 2006;54.
16. Lim S, Roche N, Oliver BG, Mattos W, Barnes PJ, Fan Chung K. Balance of matrix metalloprotease-9 and tissue inhibitor of metalloprotease-1 from alveolar macrophages in cigarette smokers: regulation by interleukin-10. *American journal of respiratory and critical care medicine* 2000;162(4):1355-60.
17. Reilly JM, Ruhin BG, Thompson RW, Allen BT, Flye MW, Anderson CB, et al. Revascularization of the solitary kidney: a challenging problem in a high risk population. *Surgery* 1996;120(4):732-7.
18. Morgan-Hughes G, Marshall AJ, Roobottom C. Flash pulmonary oedema: accurate evaluation of the renal arteries with multislice computed tomography. *Heart (British Cardiac Society)* 2003;89(10):1251-2.
19. Behar JV, Nelson RC, Zidar JP, DeLong DM, Smith TP. Thin-section multidetector CT angiography of renal artery stenosis. *American Journal of Roentgenology* 2002;178(5):1155-9.
20. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *Jama* 2007;298(3):317-23.
21. Sharifkazemi MB, Zamirian M, Aslani A. Flash pulmonary edema heralding renal artery spasm. *Cardiology* 2008;109(1):66-7.
22. Oana DR, Dan CA, Dragos V. Renal Artery Stenosis and Acute Pulmonary Edema-A Possible Correlation beyond Pickering Syndrome. *J Clin Exp Cardiol* 2015;6:377.
23. Alhaddad IA, Blum S, Heller EN, Beato MA, Bhalodkar NC, Keriaky GE, et al. Renal artery stenosis in minority patients undergoing diagnostic cardiac catheterization: prevalence and risk factors. *Journal of cardiovascular pharmacology and therapeutics* 2001 Apr;6(2):147-53.
24. Rimoldi SF, de Marchi SF, Windecker S, Meier B, Allemann Y. Screening renal artery angiography in hypertensive patients undergoing coronary angiography and 6-month follow-up after ad hoc percutaneous revascularization. *Journal of hypertension* 2010 Apr;28(4):842-7.
25. Rimoldi SF, Yuzefpolskaya M, Allemann Y, Messerli F. Flash pulmonary edema. *Progress in cardiovascular diseases* 2009 Nov-Dec;52(3):249-59.
26. Ghaffari S, Sohrabi B, Siahdasht RB, Pourafkari L. Prevalence and predictors of renal artery stenosis in hypertensive patients undergoing coronary angiography. *Hypertension research : official journal of the Japanese Society of Hypertension* 2009 Nov;32(11):1009-14.
27. Leandri M, Lipiecka J, Lipiecka E, Hamzaoui A, Amonchot A, Mansour M, et al. [Prevalence of renal artery stenosis in patients undergoing cardiac catheterization: when should abdominal aortography be performed? Results in 467 patients]. *Journal de radiologie* 2004 May;85(5 Pt 1):627-33.
28. Aqel RA, Zoghbi GJ, Baldwin SA, Auda WS, Calhoun DA, Coffey CS, et al. Prevalence of renal artery stenosis in high-risk veterans referred to cardiac catheterization. *Journal of hypertension* 2003 Jun;21(6):1157-62.
29. Pelta A, Andersen UB, Just S, Baekgaard N. Flash pulmonary edema in patients with renal artery stenosis--the Pickering Syndrome. *Blood Press* 2011 Feb;20(1):15-9.
30. Bloch MJ, Trost DW, Pickering TG, Sos TA, August P. Prevention of recurrent pulmonary edema in patients with bilateral renovascular disease through renal artery stent placement. *American journal of hypertension* 1999 Jan;12(1 Pt 1):1-7.