

**Role of furosemide stress test as a novel assessment of tubular function in acute kidney injury**Yousry Elsaied Rezk<sup>1</sup>, Ahmed Hamdy Abd El-Rahman<sup>2</sup>, Ashraf Mostafa Elnahas<sup>1</sup> and Mohamed Hatem Onsi<sup>3</sup><sup>1</sup>Cardiothoracic Surgery Department, Faculty of Medicine, Benha University, Egypt<sup>2</sup>Anesthesia and intensive Care Medicine Department, Faculty of Medicine, Benha University, Egypt<sup>3</sup>Critical Care Medicine, Faculty of Medicine, Benha University, Egypt[onsi\\_mohamed@yahoo.com](mailto:onsi_mohamed@yahoo.com)

**Abstract: Introduction:** Acute kidney injury has a high morbidity and mortality outcome so need highly sensitive marker to assess the degree of tubular affection for early detection and management to prevent further complication. **Methods:** We investigated the ability of a furosemide stress test (FST) (one-time dose of 1.0 or 1.5 mg/kg depending on prior furosemide-exposure) to predict the development of AKIN Stage-III in critically ill subjects with early AKI which considered group I. and group II who received standard management for AKI. **Result:** We studied 80 subjects; 40 consecutive patients in group I and 40 consecutive patients in group II; 25 (37.5%) and (50%) met the primary endpoint of progression to AKIN-III in group I, II consequently. patients with progressive AKI had significantly lower urine output following FST in the first 6 hours ( $p < 0.033$ ). The area under the receiver operator characteristic curves for the total urine output over the first 2 hours following FST to predict progression to AKIN-III was 0.87 ( $p = 0.001$ ). The ideal-cutoff for predicting AKI progression during the first 2 hours was a urine volume of less than 325mls with a sensitivity of 87.1% and specificity 84.1% in group I and 95% sensitivity and 95% specificity in group II. **Conclusion:** The FST in patients with early AKI serves as a novel assessment of tubular function with predictive capacity to identify those patients with severe and progressive AKI. Future studies to validate these findings are warranted.

[Yousry Elsaied Rezk, Ahmed Hamdy Abd El-Rahman, Ashraf Mostafa Elnahas and Mohamed Hatem Onsi. **Role of furosemide stress test as a novel assessment of tubular function in acute kidney injury.** *N Y Sci J* 2017;10(11):16-21]. ISSN 1554-0200 (print); ISSN 2375-723X (online). <http://www.sciencepub.net/newyork>. 3. doi:[10.7537/marsnys101117.03](https://doi.org/10.7537/marsnys101117.03).

**Keywords:** Role; furosemide; stress; test; novel; assessment; tubular; function; acute kidney injury

**1. Introduction**

Acute kidney injury (AKI) is a common complication of critical illness, seven to ten percent of intensive care units patients present with AKI during their ICU stay (1).

45-60% of them are associated with high mortality (2).

An early detection of adult patients with acute kidney injury may provide the opportunity to treat and prevent the extension of kidney injury. (1).

It is important to prevent and early management of even the mildest forms of ARF to preserve renal functions, to prevent complications of ARF and to prevent the need for chronic dialysis (2).

Acute kidney injury (AKI) is a clinical syndrome that is associated with significant morbidity and mortality [1, 2]. The incidence of acute kidney injury (AKI) has doubled in the past decade and is expected to continue increasing [3].

Patients with acute kidney injury (AKI) are cared for by a multitude of specialists including but not limited to: emergency medicine physicians, Patients who develop acute kidney injury (AKI) often require renal replacement therapy (RRT), however clinicians often disagree about the optimal timing of the initiation of renal replacement therapy (RRT) [3].

During the Acute Kidney Injury Network (AKIN) multi-disciplinary consensus meeting, the question that was ranked highest was “When renal replacement therapy (RRT) should be initiated? [4]. Renal replacement therapy (RRT) is an invasive procedure with inherent risks, and one would not want to initiate this therapy if renal function is expected to improve without intervention. [5]. Because serum creatinine and oliguria are often late signs of significant acute kidney injury (AKI), more sensitive diagnostic tests are required [6-9]. This clinical need has led to the development of multiple candidate acute kidney injury (AKI) biomarkers [6, 8-10]. Because acute kidney injury (AKI) biomarker levels change over time depending on the timing and severity of injury [9], a functional assessment of renal function might enhance biomarker performance. Since most common form (s) of intrinsic acute kidney injury (AKI) involve acute tubular injury, FST was proposed for the assessment of renal tubular function.

**2. Material and methods:**

We assembled two separate groups of critically ill patients with that were given a standardized dose of furosemide and standard management and assessed their response and outcomes.

**Group I**

40 consecutive patients with AKIN I & II was included in the study which was performed in Nasser institute intensive care unit with the goal of testing the diagnostic and prognostic accuracy of previously described and novel AKI biomarker and line of management. we included the patients who fulfilled the study criteria and received FST dose.

**Group II**

40 consecutive patients with AKIN I & II was included in the study which was performed in Nasser institute intensive care unit with the goal of testing the diagnostic and prognostic accuracy of previously described as line of management. We included the patients who fulfilled the study criteria and received standard management.

Study criteria (both group I & II)

**Inclusion Criteria:** (1) age greater than 18 admitted in an ICU, (2) AKIN stage I (6 hours of oliguria [ $< 0.5$  ml/kg/hour] or  $0.3$  mg/dL rise in serum creatinine, or, increase in 150-200% above baseline serum creatinine) OR, AKIN stage II (12 hours of oliguria [ $< 0.5$  ml/kg/hour] or increase in 200-300% above baseline serum creatinine) (3) indwelling bladder catheter (4) presence of granular or epithelial cell casts on urine sediment [defined by GW USS  $>2$ ] OR afractional excretion of sodium (FeNa)  $> 1.0\%$ , (5) treating clinical team deemed the patient to be well-resuscitated.

**Exclusion Criteria:** (1) Baseline eGFR $< 30$  ml/min/1.73m<sup>2</sup>, (2) history of renal allograft, (3) known pregnancy, (4) evidence of obstructive uropathy [e.g. hydronephrosis], (5) evidence of active bleeding, (6) patients with allergy or known sensitivity to loop diuretics, (7) achievement of AKIN stage III criteria, or (8) evidence of volume depletion at the time of furosemide administration.

**Study procedure**

40 consecutive patients who fulfilled inclusion criteria were considered study group, the next 40 consecutive patients were considered control group.

Study group (Group I): 40 consecutive patients received furosemide stress test dose.

Control group (Group II): 40 consecutive patients received standard management of AKI.

Our results will be presented under the following topics with comparing both groups.

*Demographic data (age-sex), Co-morbidities (hypertension-diabetes-ischemic heart disease, Clinical parameters (blood pressure-central venous pressure-urine output within 6 hours of management).*

*Lab measurement (urea, serum creatinine-estimated GFR-electrolytes) within 3daysafter inclusion in the study, Side effects occurring in both groups. Outcome parameters (-progression to*

*AKINIII, need for dialysis and length of stay in ICU and mortality).*

**Out come**

1. The primary outcome was the progression to AKIN III after FST dose in group I and standard management in group II.

2. The secondary outcome was the composite of achieving stage AKIN III or intra hospital death.

**Statistics**

Data were coded and entered using the statistical package SPSS version 22. Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using the non-parametric Mann-Whitney test. For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5. ROC curve for detection of progress using total urine output was constructed and area under curve analysis performed to get the best cutoff value. P-values less than 0.05 were considered as statistically significant.

**3. Result and Discussion**

In our study the age mean in group I is  $55.8 \pm 12.63$  with range from 22 years to 76 years while in group II the age mean is  $55.28 \pm 15.89$  with range from 19 years to 85 years.

While in group I males were 22 representing about 55% & females were 18 about 45% but in group II males were 28 representing about 70% & females were 12 about 30% with no statistical difference (p value= 0.166).

And in group I there were 23 hypertensive patients representing 57% while in group II there were 30 hypertensive patients 75% with no significant difference. But regarding diabetes we found that group I there was 23 diabetic patients 57.5% while in group II there were 15 diabetic patients representing 37% with no significant difference. While concerning ischemic heart diseases in group I there was 11 ischemic patients about 27.5% but in group II there were 12 ischemic patients about 30% with no significant difference.

In our study we found that in group I the mean of mean arterial blood pressure was  $84.86 \pm 11.49$  with range from 66.7 to 110 mmHg but in group II the mean was  $83.64 \pm 10.34$  with range from 66.7 to 103.3 mmHg with no significant difference. But regarding to CVP the mean was  $11.15 \pm 3.74$  with range from 5 to 19 cmh<sub>2</sub>o in group I while in group II mean was  $9.58 \pm 3.23$  with range from 5 to 15 cmh<sub>2</sub>o with no significant difference.

In our study we found that the most significant difference in urine output between group I & group II is found to be on the 1<sup>st</sup>, 2nd hours and cumulative urine but there is no difference between the two groups in the following hours, also we found that the mean value of urine output in the first 6 hours is increasing with time hour by hour in group I there is significantly decrease in amount of urine output in group II than in group I.

And the only significant creatinine difference between the two groups were on the day 1 after admission with significant p value = 0.031. Also we found that there is progressive decrease in creatinine levels in the two groups but with more decline in group I than group II.

And there is highly significant difference between the 2 groups as the p value = 0.002 as in group I the mean of GFR is  $15.78 \pm 7.42$  while the mean in group II is  $11.17 \pm 7.73$  which means that GFR is improved in patients receiving frusemide more than patients standard management.

And there is no significant difference between 2 groups in any side effects including all electrolyte

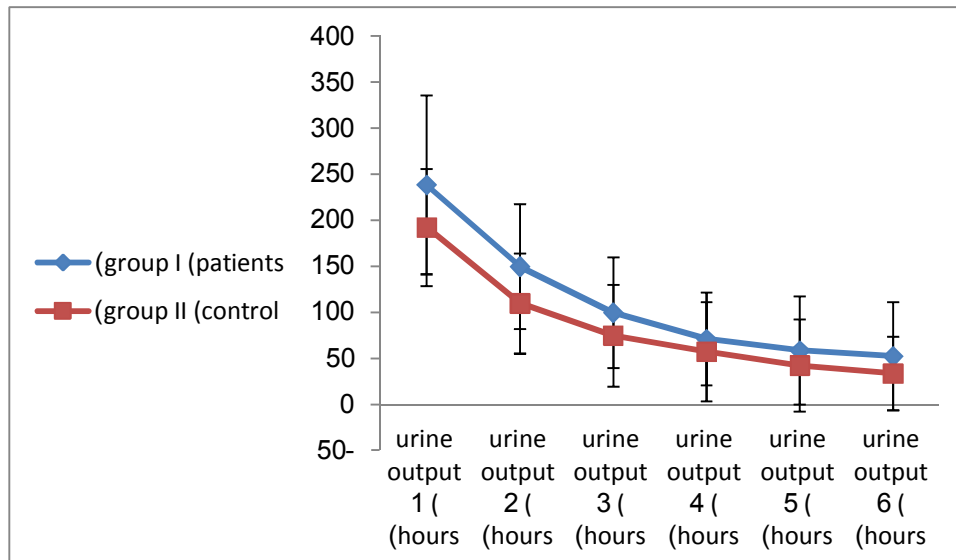
disturbance except in hypotension as there is highly significant difference between 2 groups as p value = 0.001. In group I there are 11 patients representing 27.5% who suffered from hypotension as side effect for using frusemide stress test but in group II there is no patients suffering from hypotension at all which indicates that using frusemide in treatment of acute kidney injury may cause hypotension as side effect.

As regards progression in group I, 15(37.5%) patients progressed to AKIN III while in group II, 20 (50%) patients progressed to AKIN III representing about 50%. There is no statistically significant difference between 2 groups (p value=0.260).

Regarding length of intensive care unit there was no significant difference between 2 groups in length of stay as the mean in group I is  $4.81 \pm 1.85$  with range from 3 to 10 days but the mean in group II is  $4.8 \pm 2.38$  with range from 3 to 14 days, And mortality in group I there was 5 (12.5%) patients who died while in group II there was only one patient (2.5%) who died, there is no statistically significant difference between 2 groups (p value= 0.201).

		group I (patients)		group II (control)		P value
		Count	%	Count	%	
Htn	positive	23	57.5%	30	75.0%	0.098
	negative	17	42.5%	10	25.0%	
DM	positive	23	57.5%	15	37.5%	0.073
	negative	17	42.5%	25	62.5%	
IHD	positive	11	27.5%	12	30.0%	0.805
	Negative	29	72.5%	28	70.0%	
hypotension	positive	11	27.5%	0	.0%	< 0.001
	negative	29	72.5%	40	100.0%	
hypokalemia	positive	6	15.0%	5	12.5%	0.745
	negative	34	85.0%	35	87.5%	
hypomagnesemia	positive	22	55.0%	16	40.0%	0.179
	negative	18	45.0%	24	60.0%	
hypophosphatemia	positive	1	2.5%	1	2.5%	1.000
	Negative	39	97.5%	38	95.0%	
	hypomagnesemia	0	.0%	1	2.5%	
Gender	Female	18	45.0%	12	30.0%	0.166
	male	22	55.0%	28	70.0%	
Mortality	negative	35	87.5%	39	97.5%	0.201
	positive	5	12.5%	1	2.5%	
Progress	negative	25	62.5%	20	50.0%	0.260
	positive	15	37.5%	20	50.0%	

	Group I					Group II					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	55.80	12.63	58.00	22.00	76.00	55.28	15.89	59.00	19.00	85.00	0.946
urine output (6 hours)	671.25	342.48	600.00	100.00	1500.00	518.75	271.67	500.00	200.00	1200.00	0.033
Kidney functions tests OA	4.53	2.52	3.60	2.20	13.00	6.43	3.63	6.50	1.30	17.00	0.009
Kidney functions tests 1	4.12	2.42	3.35	1.50	12.20	5.12	2.50	5.25	1.20	11.00	0.031
Kidney functions tests 2	3.69	1.88	3.25	1.20	9.80	4.30	2.13	4.20	1.00	10.00	0.145
Kidney functions tests 3	3.16	1.97	2.45	1.00	10.50	3.45	1.73	3.15	.90	8.20	0.242
NA	135.00	9.20	135.50	120.00	165.00	132.92	8.77	131.00	121.00	157.00	0.223
K	4.93	1.04	4.80	2.70	7.20	4.79	1.27	4.70	1.60	8.20	0.531
Mg	2.11	.46	2.00	1.30	3.50	2.28	.41	2.20	1.40	3.20	0.059
PH	4.03	1.52	4.00	1.80	9.20	5.22	1.55	5.15	3.00	10.00	<0.001
SBP	118.52	12.02	120.00	95.00	142.00	111.75	11.30	110.00	90.00	130.00	0.015
DBP	68.70	12.33	68.00	50.00	94.00	70.25	10.74	70.00	50.00	90.00	0.492
CVP	11.15	3.74	11.50	5.00	18.00	9.58	3.23	10.00	5.00	15.00	0.062
LOS	4.81	1.85	4.00	3.00	10.00	4.80	2.38	4.00	3.00	14.00	0.621



**Furosemide stress test characteristics**

We assessed the urine flow rate in response to furosemide. The Maximum UFR was within the first two hours. We compared the UFR between the two

groups for each hourly interval; group II had a lower UFR response compared to group I (p< 0.026).

We tested various combinations of the UO intervals to assess, which had the best discriminative capacity. We found that the sum of the first two hours

of UO after the FST had the highest AUC to predict the primary outcome (0.84 in group I), (93% in group II) We also assessed the sensitivity and specificity of various two hour urine volumes to predict the outcomes. The two hour UO of 325 ml or less had the best sensitivity and specificity to predict the primary outcome.

As regards urine output our study demonstrated that diuresis was maximum within first two hours after inclusion This is in concordance with **Lakhmir et al 2013** who found that maximum diuresis was in 2<sup>nd</sup> and 3<sup>rd</sup> hours and **Koyner 2015** who found that maximum diuresis was in first two hours also [6], And **Shilliday et al 1997** found that maximum UFR was after first 6 hours of first day of furosemide.

In our study the most significant difference in urine output between group I & group II was found to be on the 1<sup>st</sup> & 2<sup>nd</sup> hours after inclusion as well as cumulative UOP after 6 hours but there was no difference between the 2 groups in the following 4 hours.

Upon addressing serum creatinine level, our study showed that gradual decline in both groups over three days with statistical significance only demonstrated as more decline in group I vs. group II on day one, however **Shilliday et al 1997** and **Morgan et al 2011** stated that the significant improvement in creatinine was on 2<sup>nd</sup> day after receiving furosemide.

Similarly GFR showed progressive improvement in our study in follow up period with no significant difference between the two groups which agreed with **koyner et al 2015** and **Samual et al 1994** who stated that GFR showed progressive improvement after receiving either high dose of furosemide vs. standard management with no significant difference.

As regards side effects noticed in both groups; hypotension occurred only in group receiving FST dose in contrast with **Lakhmir et al 2013** where he reported no incidence of hypotension whereas none was seen in group II with P value (0.001).

On the other hand hypokalemia was noticed in six patients in group I vs. five patients in group II. **Greenberg 2000** stated that hypokalemia tend to occur more in patients receiving FST dose non the less no statistically significance difference concerning hypokalemia was noticed between the two groups in our study. **Adroque Hj Madias 2000** stated that hyponatremia occurred more frequently with FST dose; however no patient included in our study suffered from this side effect.

Outcome parameters in our study included progression to AKINIII & need for dialysis, length of ICU stay & mortality.

As for progression of AKI, our study found that group II showed a higher tendency of progression than group I however there was no significant difference.

Various studies stated that UOP within two hours predict the progression to AKINIII & dialysis as **Lakhmir et al 2013** found that the sum of the first 2 hours of UOP after the FST had the highest AUC to predict the primary outcome (0.87). He also assessed the sensitivity and specificity of various 2-hour urine volumes to predict the primary and secondary outcomes (progression to AKINIII-dialysis). The 2-hour UO of 200 ml had the best sensitivity and specificity to predict the progression to AKINIII & dialysis.

In our study we could determine a cut point for detection of the progression which was in group I (325 ml ) with sensitivity 84% & specificity of 93.3% with high significance (p= 0.001), and in group II was ( 325 ml) with sensitivity 84% & specificity of 86% with high significance ( p value = 0.001) in the first two hours.

Also **Koyner 2015** found that UOP within two hours was good predictor of progression to AKINIII & need for dialysis or not. [6]

In concordance with **Chawla et al 2013** and **HO KM, Sheredan Dj 2006** found that sustained urinary output response to furosemide at the early stage of AKI may be considered as a 'proxy' for having a mild AKI and has a lower of risk of requiring dialysis.

This was in adverse to **Iqbal and Akbar 2014** shows no effect of higher doses of furosemide on preventing the progression to AKINIII. And **Mehta 2010, Uchino 2004** who even stated that furosemide increases the risk of progression to AKINIII & dialysis.

Concerning length of ICU stay our study found that there was no statistically significant difference between the two groups in length of ICU stay Which was in concordance with **Kwork et al 2006** and **Iqbal and Akbar 2014** who stated that there was no significant difference of higher dose of furosemide in shorting the length of ICU stay.

This was discordance with **Annika et al 2006** who found that the mean of length of stay was significantly shorter in the group who received FST dose.

In our study we found that in group I there were 5 patients who died representing (12.5 %) while in group II there was only one patient who died representing (2.5 %), but there was no statistically significant difference between both groups.

That was in concordance with **Shilliday et al 1997** and **Iqbal and Akbar 2014** and **HO KM, Sheredan 2006** who found that there was no significant difference in decreasing the incidence of mortality in patients received higher doses of

furosemide. And discordance with **Mehta 2010**, **Uchino 2004** who found that furosemide increases the risk of intra hospital mortality. While **Koyner 2015** found that FST was good indicator of mortality [6].

#### 4. Conclusion

In summary, the FST is a novel dynamic functional assessment of tubular function that has good predictive capacity to identify those patients that will progress to advanced stage AKI, Furosemide has no brevedge on standard management in treatment of early stages of AKI.

#### Key messages

The performance of the FST to predict the primary outcome was robust and consistent with a range in ROC AUC of 0.84- 0.86.

- a) Patients should be euvolemic before undertaking any type of furosemide challenge, and that volume replacement is mandatory in patients who are not obviously volume overloaded.
- b) FST should be conducted in an appropriate clinical setting where UO, heart rate, and blood pressure can be monitored frequently.
- c) FST is a novel dynamic functional assessment of tubular function that appears to have good predictive capacity to identify those patients that will progress to advanced stage AKI. Further validation studies of the FST are warranted.

#### References

1. Bellomo R, Kellum JA and Ronco C: Acute kidney injury. *Lancet*; 2012: 380: 756-766.
2. Coca SG, Singanamala S and Parikh CR: Chronic kidney disease after acute kidney injury:

a systematic review and meta-analysis. *Kidney Int.*; 2012: 81: 442-448.

3. Hsu RK, McCulloch CE, Dudley RA, et al: Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol.*; 2013: 24: 37-42.
4. Gibney N, Hoste E, Burdmann EA, et al: Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. *Clin J Am Soc Nephrol.*; 2008: 3: 876-880.
5. Seabra VF, Balk EM, Liangos O, et al: Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. *Am J Kidney Dis.*; 2008: 52: 272-284.
6. Koyner JL, Garg AX, Coca SG, et al: Biomarkers predict progression of acute kidney injury after cardiac surgery. *J Am Soc Nephrol.*; 2012: 23: 905-914.
7. Chawla LS and Kellum JA: Acute kidney injury in 2011: Biomarkers are transforming our understanding of AKI. *Nat Rev Nephrol.*; 2012: 8: 68-70.
8. Bonventre JV: Diagnosis of acute kidney injury: from classic parameters to new biomarkers. *Contrib Nephrol.*; 2007: 156: 213-219.
9. Devarajan P: Emerging biomarkers of acute kidney injury. *Contrib Nephrol.*; 2007: 156: 203-212.
10. Doi K, Noiri E and Sugaya T.: Urinary L-type fatty acid-binding protein as a new renal biomarker in critical care. *Curr Opin Crit Care.*; 2010: 16: 545-549.

10/31/2017