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Evaluation of Renal Function in Patients with Acute Heart Failure Through Dynamic Scintigraphy Examination. A pilot study

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Abstract

The Acute Decompensated Heart Failure National Registry (ADHERE) has shown that approximately 30% of patients hospitalized for acute heart failure exhibit acute or chronic renal insufficiency [1]. The development of heart failure (HF) is often observed in patients with chronic kidney disease (CKD), and HF prevalence significantly increases in cohorts with declining GFR. The best diagnostic technique used to assess renal function through the administration of radiopharmaceuticals is renal scintigraphy. The results obtained through scintigraphy pertain to the total GFR, the contribution of individual kidneys to it, and changes in renography curves, all in the short term. From the clinical data obtained an increase in GFR values, there was a mean increase of 10.392 ml/min in GFR, following treatment with 1.4% hypertonic saline and furosemide. These results are certainly very encouraging although in a small patient group and require further investigation. Therapy with 1.4% hypertonic saline plus furosemide improves the clinical conditions and prognosis of patients with acute congestive heart failure associated with a deterioration in renal function and should be used in clinical practice.

Keywords: Renal Function; GFR; Nuclear Medicine Scintigraphy; Heart Failure; Hypertonic Saline Solution

Introduction

Heart failure is a serious current health problem, and the prognosis for affected patients is generally unfavorable. It often coexists with a series of comorbidities, among which the reduction of renal function is particularly relevant, as a decrease in glomerular filtration rate (GFR) independently predicts mortality and accelerates the overall progression of cardiovascular disease. Prognosis also varies based on the timing of the onset of functional decline, with acute renal function decline associated with a higher mortality rate compared to a progressive decline [2-4]. Renal impairment is one of the most powerful predictors of a poor clinical outcome in heart failure (HF). The risk of death in patients with reduced glomerular filtration rate (GFR) is more than double that of patients without renal impairment. In addition, a decline in eGFR (irrespective of cause) is associated with a 60–80% higher mortality.

Renal function decline is a common consequence in these patients and serves as a strong independent risk factor for adverse outcomes. Both Acute Kidney Injury (AKI) and worsening renal function (WRF) lead to hospitalization, prolonged hospital stays, and death. This requires the search for an effective therapy to counteract renal function decline in heart failure patients. For monitoring renal function, sequential renal scintigraphy has been chosen for its immediate feedback. The following study highlights the contribution as diagnostic technique of sequential renal scintigraphy [4].

The current study aims to evaluate these patients in the short term, with a future focus on long-term assessment and the role of hypertonic saline solution plus furosemide therapy in achieving to improve the clinical conditions and prognosis of patients with congestive heart failure associated with a decline in renal function.

Sequential Renal Scintigraphy

The renal scintigraphy, also known as, nuclear renal scan is an imaging method that uses radiopharmaceuticals/radiotracers to evaluate renal anatomy, physiology, and pathology [5].

These act as tracers through which it is possible to quantify the Glomerular Filtration Rate (GFR), renal plasma flow, and tubular function. Commonly used techniques include static and dynamic renal scintigraph. The former allows the study of functioning renal tissue, as it will be the only one capable of capturing the radiopharmaceutical; the latter exploits the ability of some of these drugs to be taken up and eliminated by the kidneys in proportion to residual renal function. The technique of interest is dynamic or sequential renal scintigraphy. This represents the method of choice in clinical practice as it allows for the quantitative assessment of overall renal function with almost immediate timing, the contribution of individual kidneys, and simultaneously visualizes the organ of interest. It offers unique advantages over other diagnostic techniques and presents minimal risks, as the radiation dose that the patient receives is minimal, as the risk of severe allergic reactions to the drugs used.

Hypertonic Solution and Furosemide Therapy

The treatment utilized involves the infusion of 1.4% hypertonic saline solution, the effectiveness of which has been widely demonstrated in conditions where blood flow is compromised, along with furosemide. Intravenous infusion of hypertonic saline solution rapidly increases the plasma sodium concentration and consequently plasma osmolality, mobilizing fluids from the extravascular to intravascular space and thereby increasing renal plasma flow. In this condition, an increase in peritubular hydrostatic pressure occurs, leading to an increase in urinary excretion. This pathophysiological mechanism allows not only to improve the Glomerular Filtration Rate (GFR) and diuretic efficiency but also to ensure a reduction in plasma renin and aldosterone levels. The combination with furosemide enhances its effectiveness, as the hypertonic solution increases the drug concentration in the loop of Henle, promoting its stimulating effect on sodium excretion [6-18].

Material and Methods

Twenty patients have been recruited for the study but only 9 pts (5 M - 4 F) aged from 51 to 87 year (mean age 72.5 + 12.7) accomplished protocol so long as the SARS-CoV-2 pandemic prejudiced the complete performance investigation. Patients were selected irrespective of age and KDIGO class guidelines [19-21].

Glomerular Filtration Rate (GFR) was the primary parameter studied using sequential renal scintigraphy with 99mTcMDP. Each patient served as their own control, with baseline GFR assessed through slow infusion of 125 mg furosemide into 100 ml of physiological saline.

Approximately 48 hours later, a second scintigraphy was performed, assessing GFR with the infusion of 125 mg furosemide into 100 ml of 1.4% hypertonic saline.

The imaging protocol was the same for both baseline and post-infusion renal scintigraphy, involving the use of GE Millennium large-field gamma camera, equipped with a low-energy general-purpose (LEGP) parallel-hole collimator, and positioned posteriorly to the lumbar region.

Intravenous administration of 100 MBq 99mTc-MDP and Dynamic acquisition, divided into 3 different phases after 30 minutes of radiopharmaceutical administration. The acquisition matrix was 64x64. The three phases of image acquisition were:

- First pass: one frame per second for one minute to highlight the initial passage of the radiopharmaceutical with renal perfusion.
- Second phase: one frame every 10 seconds for the following 4 minutes to assess the parenchymal extraction of the radiopharmaceutical.
- Third phase: one frame every 20 seconds to study the renal secretion of the radiopharmaceutical.

The processing of the obtained data was carried out thanks to the activity/time curves obtained from renal and subrenal ROIs, manually drawn on the images obtained at the time of parenchymal accumulation of the radiopharmaceutical, as in this phase, it is possible to better recognize the renal margins. Subsequently, the background renal curves were subtracted from the renal ones, thus obtaining renography curves that describe renal function in its phases of perfusion, extraction, and excretion. Through these curves, it is possible to extrapolate some quantitative indices,

of which the one that has been most focused on is the index of parenchymal function relative to each kidney. This index is calculated based on integral counts at the 2nd/3rd minute and is expressed as a percentage of the overall function of the kidney.

The calculation of the GFR value was performed using the Gates formula [22]. This formula is based on the calculation of integral renal counts at the third minute, the moment when the tracer bolus passes through the kidneys. These renal counts are related to the background activity and corrected for tissue attenuation, calculated in turn using the formula, which is based on the patient's weight and height. To calculate the GFR, the following steps will be essential: recording the patient's height and weight and measuring the dose, i.e., the activity injected into the patient. To obtain this dose, it is important to use the same gamma camera used for the examination, performing a static scintigraphy acquisition of the syringe containing the activity that will be injected into the patient vein and of the remaining activity after the injection. This method presents some indeterminacy factors resulting from integral calculations, the variability of renal and background ROIs, and standardized correction for renal depth.

Procedure of execution

To initiate the procedure, the patient only needs to be adequately hydrated, and fasting is not required. The examination is commonly performed with the patient in a supine position, utilizing a gamma camera positioned at the lumbar region (Figure 1). Landmarks are employed to include the kidneys in the gamma camera's field of view, and adjustments can be made for ptotic or ectopic kidneys. The reference points used include the xiphoid projection at the upper margin, the costal arch, and the iliac crest outlining the central region, with the pubis marking the lower margin. Afterward, the radiopharmaceutical is injected intravenously, and image acquisition begins immediately after the injection. Several frames are recorded consecutively, with a constant or variable duration, depending on the drug distribution. The image capture occurs in three phases:

1. Perfusion Phase: Corresponding to the first minute of acquisition.

2. Parenchymal Phase: The drug accumulates in both kidneys, outlining the renal parenchyma.

3. Excretion Phase: The drug accumulates in the renal calyces and pelvis from the first three minutes.

This procedure has a total duration of approximately half an hour.

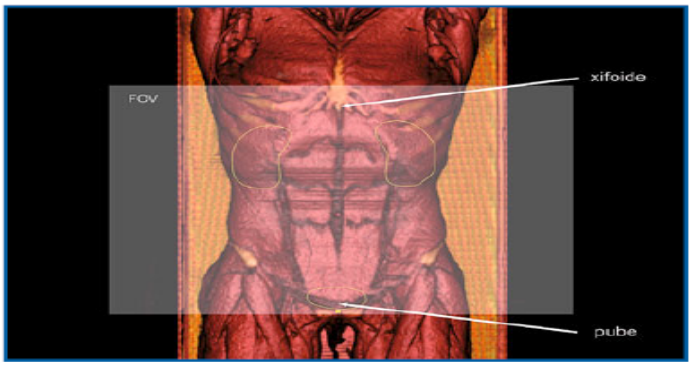

Figure 1: Representation of the Correct Field of View (FOV). Positioning in Dynamic Renal Scintigraphy.

The standard processing involves the use of activity/time curves obtained from renal regions of interest (ROI), extracted through automatic or semi-automatic software. (Figure 2)

Once generated, the activity/time curves of the background are subtracted from those of the kidneys, yielding the socalled renography curves or renograms, which reflect the distribution of the radiopharmaceutical:

- Vascular Phase: Known as the first pass, characterized by a rapid ascent.
- Parenchymal Phase: Exhibits a slower rise, expressing glomerular or tubular function through renal extraction of circulating radioactivity.
- Excretion Phase: Described by a descending curve that depicts the outflow of radioactive urine.
- The study of these curves allows for the extraction of quantitative indices and the assessment of glomerular filtration.

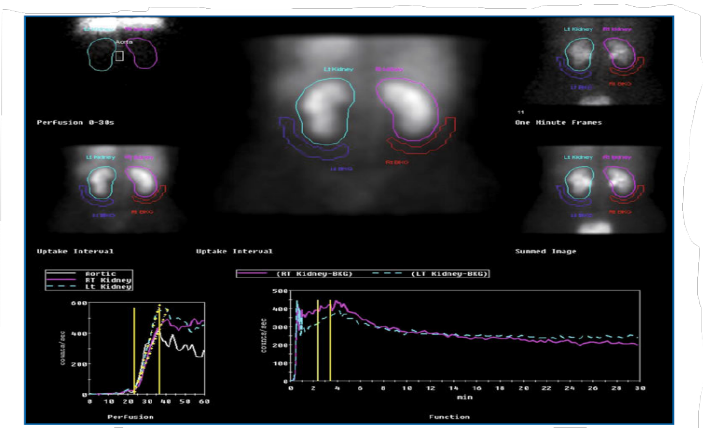

Figure 2: Dynamic Renal Scintigraphy Processing

The central image illustrates the renal parenchymal accumulation phase, with renal and background regions of interest (ROI) outlined. The top-left image corresponds to the excretion phase, while the top-right image is related to the parenchymal accumulation phase. In the bottom-left section, activity/time curves of the vascular phase are presented, with yellow indicating the boundaries of the onset and peak vascular phases. The bottom-right section depicts the two renograms.

Quantitative Indices

These indices are numerous and are derived from abnormalities in the renogram. Among these, we recognize:

- Peak parenchymal time: it represents the time needed to reach maximum parenchymal activity, for which under normal conditions, 5 minutes are required from the injection. This could be altered if the drug is retained at the level of the calyces and renal pelvis.
- Relative uptake: Calculated a few minutes after drug administration, using integral calculations on the Regions of Interest (ROI).
- Ratio of radioactivity at 20 minutes to peak radioactivity: The decay of renal function causes an abnormality in the curve, and the degree of this abnormality can be quantified by measuring residual cortical activity.
- Excretion halftime: The time required for counts to halve during the excretion phase.
- Relative parenchymal function index for each kidney: Expressed as a percentage of the overall function and calculated based on integral counts over a specific time interval.

Calculation of GFR

Sequential renal scintigraphy with 99mTc-DTPA is the most used technique for calculating the overall and separate GFR for each kidney. A widely used calculation method is the Gates method, which requires recording the patient's weight and height and measuring the activity of the injected dose. This enables the estimation of clearance by evaluating the quantity of the drug after 60- and 180-minutes post-injection. Careful attention is necessary for this process, including recording the injection time and the blood sampling time, which should not be contaminated by substances such as heparin or saline solution. The assessment of dose activity is performed using the gamma camera by Gates' Formula (22).

$$GFR = \frac{\frac{cpm_{rene\cdots dx}}{e^{-0{,}153\cdot[13{,}3\cdot(Peso/Altezza)+0{,}7]}} + \frac{cpm_{rene\cdots sn}}{e^{-0{,}153\cdot[13{,}2\cdot(Peso/Altezza)+0{,}7]}}}{Dose} \times 100 \times 9{,}75621 - 6{,}19843$$

Data analysis

For the study group, various parameters obtained from baseline and post-infusion renal scintigraphy were compared, and these were further correlated with patient age and KDIGO classification.

The average age of the study group patients is 72.2 years (SD + 13.99). The maximum age is 87 years, and the minimum age is 51 years. The sample consists of 55.55% women and 44.45% men.

Renal Scintigraphy - Baseline Results (Table 1): The mean baseline Glomerular Filtration Rate (GFR) for the study participants is (47.01 + 17.84). The average contribution from the right kidney is 29.49 +8.85), and from the left kidney is (22.60 + 9.60). Regarding the renography curves of both kidneys in all patients, except for one, a more or less significant reduction in the glomerular filtration phase was observed:

	Total GFR (ml/min)	Right kidney (ml/min)	Left Kidney (ml/min)
Mean + SD	47,01+17,84	29,49+8,85	22,60+9,60
Minimum value	15,03	6,76	8,26
Maximum value	73,57	38,25	35,31

Table 1: Basal GFR (ml/min) in the study population

The patients were divided into groups based on the renal function classes derived from the KDIGO guidelines (21) as follow: 0 pts belong to KDIGO class 1; 2 pts belong to KDIGO class 2; 4 pts belong to KDIGO class 3A; 1 pts belongs to KDIGO class 3B; 2 pts belong to KDIGO class 4; and 0 pts belong to KDIGO class 5

Renal scintigraphy post-infusion (Table 2). The mean GFR obtained through post-infusion renal scintigraphy is (51.77+ 24.12). The average change compared to baseline GFR is (10.39 +12.47). The mean GFR value for the right kidney is (30.36 + 11.88), and the mean GFR value for the left kidney is (27.15 + 13.06). All patients benefited from the therapy with an increase in GFR, except for one (p=0.00263; t-test=0.005936). The evaluation of renal curves shows an improvement in the glomerular filtration phase in 6 out of 9 patients.

	Total GFR (ml/min)	Right Kidney (ml/min)	Left Kidney (ml/min)	Variation (ml/min)
Average + SD	51,77 +24,12	30,36 +11,88	27,15 +13,06	10,39 +12,47
Minimum Value	21,99	11,43	10,73	0
Maximum Value	103,5	51,75	37,80	41,67

Table 2: Statistics related to values obtained through post-infusion renal scintigraphy.

The categorization of patients into KDIGO classes based on post-infusion; GFR values also occurred after the second scintigraphy, although there were few specifically changes in class as follow: 1 pts belongs to KDIGO class 1, 1pts belongs to KDIGO class 2; 5 pts belong to KDIGO class 3A; 0 pts belong to KDIGO class 3B; 2 pts belong to KDIGO class 4; and 0 pts belong to KDIGO class 5. (Figure 3)

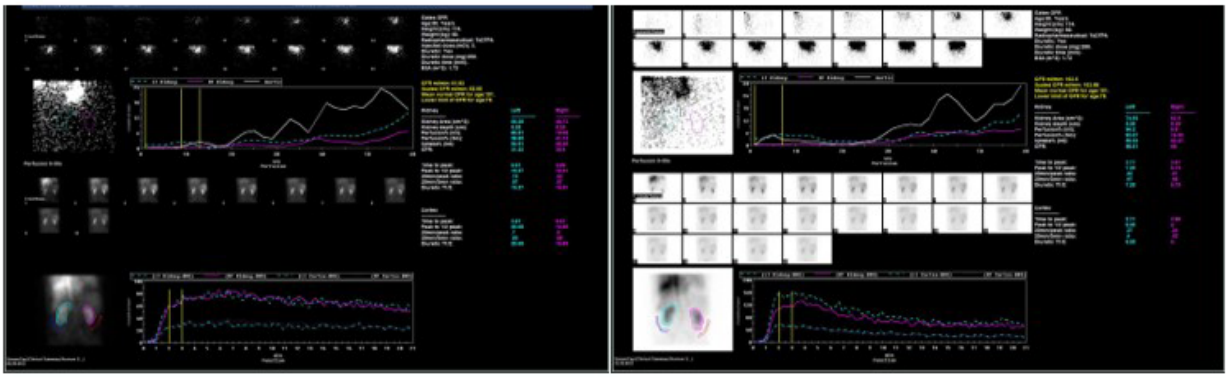

Figure 3: evaluation of GFR at baseline (a) and after hypertonic saline solution infusion (b) in a studied patient.

Discussion

From the clinical data obtained through sequential renal scintigraphy, it is evident that all patients except one experienced a short-term increase in GFR following treatment with 1.4% hypertonic saline and furosemide. Specifically, there was a mean increase of 10.39 ml/min in GFR, despite a difference of approximately 5 ml/min between the mean post-infusion GFR and the mean baseline GFR. Among these analyzed patients, only two moved to a higher KDIGO class. Notably, one patient shifted from KDIGO 2 to KDIGO 1, regaining a standard GFR value, while another moved from KDIGO 3B to KDIGO 3A. The patient who benefited the most from the treatment, entering KDIGO class 1 with a GFR increase of about 40 ml/min, is the youngest in the analyzed sample, exhibiting the highest renal performance and an equal contribution from each kidney in the glomerular filtration process. Although the result of a single patient is not statistically significant, it may suggest a future consideration that the analyzed therapy could be used with excellent results in patients at an early stage of the disease. Apart from this individual case, for other patients (all over 60), there seems to be no correlation between age and increased GFR post-infusion, and the increase in GFR occurred without gender differences.

Regarding the contribution of individual kidneys to the total GFR, it was observed that there was primarily a greater benefit from the right kidney, except for two cases, but this is not of particular clinical relevance. Analyzing the partial contribution of the kidneys, among the 9 patients examined, 6 had a greater therapeutic benefit from the kidney that contributed more to the total GFR. Considering that, according to the Tonnesen formula, the physiological ratio in the contribution to total GFR ranges between 50:50 and 43:57, only 3 of these 6 patients are outside the physiological range.

As for the renography curves, it was possible to assess that out of 9 patients, 6 experienced a recovery of glomerular filtration observed through post-infusion scintigraphy. Specifically, these patients had an increase in GFR greater than or equal to 8 ml/min, while for those with an improvement below this value, there was no change in the renography curves.

Patient data obtained through baseline scintigraphy

Patient	Total GFR (ml/min)	Right Kidney %	Right GFR (ml/min)	Left Kidney %	Left GFR (ml/min)	KDIGO Class
Pts1	15.03	45	6.76	55	8.26	4
Pts2	39.82	56	22.18	44	17.43	3B
Pts3	48.43	59	28.57	41	19.85	3A
Pts4	73.57	52	38.25	48	35.31	2
Pts5	27.3	63	17.19	37	10.1	4
Pts6	61.83	50	30,91	50	30.91	2
Pts7	53.81	50	26.9	50	26.9	3A
Pts8	46.74	52	24.3	48	22.43	3A
Pts9	57.61	44	25.34	56	32.26	3A

Patient data collected through post-infusion renal scintigraphy

Patient	Total GFR (ml/min)	GFR Variation (ml/min)	Right Kidney %	Right GFR (ml/min)	Left Kidney %	Left GFR (ml/min)	KDIGO Class
Pts1	21,99	6,96	52	11.43	48	10.55	4
Pts2	53.93	14.11	64	34.51	36	19.41	3A
Pts3	57.22	8.79	58	33.18	42	24.03	3A
Pts4	78.76	5.19	52	40.95	48	37.8	2
Pts5	29	1.7	63	18.27	37	10.73	4

Pts6	103.44	41.61	50	51,75	50	51.75	1
Pts7	58.94	5.13	50	29.47	50	29.47	3A
Pts8	56.72	9.98	50	28.36	50	28.36	3A
9Pts	57.61	0	44	25,34	56	32.26	3A

Conclusion

The study of the therapy with 1.4% hypertonic saline and furosemide brings with it the need to improve the clinical conditions and prognosis of patients with congestive heart failure associated with a decline in renal function.

The results obtained although they are preliminary and require further investigation, are certainly very encouraging. The majority of patients who participated in the study experienced an improvement in the glomerular filtration process in the short term. The choice of renal scintigraphy as a diagnostic tool allowed an immediate evaluation of the organ in question, providing more assistance compared to other diagnostic methods commonly used in clinical practice. The data currently available although they are limited encourage the entire scientific community to further explore this topic so that one day all the limitations and difficulties for both doctors and patients caused by heart failure and renal disease can be overcome.

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