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Estimation of relative bilateral renal function of potential voluntary kidney donors using various computerized tomography methods

Dr. Sunil Kumar Khoth and Dr. Ridhima Gupta

Abstract
Aims & Objectives:
a) To estimate relative renal function by four different methods in live voluntary kidney donors using computed tomography. 1. Semi-automated volume method; 2. Attenuation capacity method; 3. Modified ellipsoid method; 4. Parenchymal area method.
b) To compare the results of relative renal function estimated by the four CT methods with that estimated by Tc99m DTPA renal scintigraphy to identify the best fit CT method to determine split renal function.

Methodology: A prospective study on patients who were potential voluntary kidney donors who attended the Nephrology Out Patient Clinics for a potential renal donation.

Inclusion Criteria
1. All consecutive voluntary kidney donors who attended the Nephrology out Patient Clinics of S.P.Medical College from December 2020 to October 2021.
2. Those of the above who underwent contrast enhanced computed tomography as a part of preoperative workup in Department of Radiology in our institution.
3. Those of the above who underwent nuclear scintigraphy as a part of preoperative workup in Department of Nuclear Medicine in neighbouring nuclear medicine lab.

Results: The mean time taken was the maximum for methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), which may be attributed to the relative technical difficulty in drawing manually corrected region of interests on each slice. Based on these findings we infer that Method 3 or Relative Mean Ellipsoid Volume Method in terms of its highest correlation coefficient, very good agreement with the reference standard, technical simplicity and least time taken among the other CT methods is the best among the four CT methods to assess relative renal function. In view of the simplicity we recommend that this test can in fact be performed by the referring physician itself.

We also infer that methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), though have a very good correlation with the reference standard are limited due to the technical complexity requiring a workstation monitor and increased time consumption

Conclusion: Computed tomography (CT) due to its excellent anatomical information is an established imaging modality in the pre-operative evaluation of live potential voluntary kidney donors. Intravenous non-iodinated contrast enhanced CT of the abdomen is the current radiological investigation of choice in planning for surgery in such patients.

2. When it comes to functional assessment of live potential voluntary kidney donors renal Tc99m DTPA scintigraphy is considered a reference standard though not the gold standard. A difference of up to 7% of relative renal function does not necessarily mean significant renal functional loss. A functional difference of20% is needed to label a kidney as dominant as compared to the other kidney.

Keywords: Donor, kidney, volume, computed, evaluation, technique

Introduction

End stage renal disease is a common disease entity. Diabetes mellitus and hypertension are the most common diseases that cause end stage renal disease. The functional units of the kidneys are the nephrons. In progressive renal failure, the nephrons have an inherent capacity to function normally for many years.

But as the process of end stage renal disease evolves the nephrons are destroyed one by one. Eventually there is a stage where only twenty percentage of the nephrons function normally.

Further damage occurs in the form of the remaining nephrons undergoing compensatory hypertrophic changes. Eventually it results in termination of the abnormal nephrons. Beyond this stage the symptoms of renal disease begin to manifest. The varied symptoms of renal failure constitute uremia.

Various treatment options are there for a person with endstage renal disease. Initially the patient is managed with dietary modifications and medications. But when these are inadequate to prevent uremic symptoms then only two options remain which are dialysis and kidney transplantation.

Dialysis is further divided into chronic ambulatory peritoneal dialysis (CAPD) and intermittent haemodialysis. In CAPD the peritoneum acts as the membrane for filtration but this method is employed only for minority of the patients.

Most others are subjected to intermittent hemodialysis. This method involves extracorporeal circulation. Here the filtration happens through an external filter. This method is considered an active treatment for patients in uremia and is much more efficient than CAPD. However they are associated with severe lifestyle limitations. There is also severe reduction in life expectancy [1]

The definitive treatment option for end stage renal disease is renal transplantation [2]. Live donor kidney transplantation is the most common form of transplantation done in India. Live kidney donation is better than cadaveric transplants as the surgical procedure can be performed electively which has resulted in increased survival benefits as compared to cadaveric transplants.

Materials And Methodology

Study Design

This is a Prospective study to assess diagnostic accuracy.

Study Type

Analytical

Setting

SP Medical College is a tertiary center hospital located in the town of Bikaner, Rjasthan. This is now a 1800 bedded hospital which was established in the year 1935. The annual outpatient visits are about 0.5 million with inpatient admissions of upto 80,000. The institution also has multiple specialty and super specialty units with the Departments of Radiology, urology, nephrology and nuclear medicine among them.

Subjects

The study patients were potential voluntary kidney donors who attended the Nephrology Out Patient Clinics for a potential renal donation.

Inclusion Criteria

1. All consecutive voluntary kidney donors who attended the Nephrology out Patient Clinics of S.P.Medical College from December 2020 to October 2021.
2. Those of the above who underwent contrast enhanced computed tomography as a part of preoperative workup in Department of Radiology in our institution.
3. Those of the above who underwent nuclear scintigraphy as a part of preoperative workup in Department of Nuclear Medicine in neighbouring nuclear medicine lab.

Exclusion Criteria

All potential voluntary kidney donors selected by clinical and laboratory criteria who had,

1. Contraindications to computed tomography (CT) imaging.
2. Contraindications to use of non-iodinated intra venous contrast agent.
3. Presence of renal masses, multiple renal calculi or large polar cysts.
4. Presence of obstructive uropathy.
5. Contraindications to renal scintigraphy.

Informed Consent

The Institutional Review Board waived the need for informed consent as there was no change in the existing CT protocol for the sake of this study and measurements obtained for the sake this study would not in any way influence the patient management or delay procedures.

Sampling

The prospective study patients were referred to us from the nephrology OPD. All consecutive subjects fulfilling the inclusion criteria were enrolled in the study to avoid bias and no other specific sampling strategy was employed.

The selections of subjects were independent of the results of the reference standard (renal scintigraphy).

Timing

The index tests (CT) was performed within one week of performing the reference standard test (renal scintigraphy). It was unlikely that the target health condition would change in the interim period between the two tests.

Computed Tomography (Ct) Imaging Methods

CT scanner

The study was performed in our institution in a Siemens Syngo (Somatom Emotion) machine which is a 256 slice multi detector CT.

Patient Preparation

Standard precautions as for any patient undergoing contrast enhanced CT study was followed.

The patient was requested to be fasting for at least four hours before the scheduled timing for the scan. The patient's serum creatinine value was checked before the study and had to be less than 1.4 mg%. The patient was asked about history of allergy and asthma in which case they would advised to take Tablet. Prednisolone 30 mg, twelve and two hours before the procedure along with an oral anti histamine.

In case of previous severe contrast reactions or pregnancy there was discussion with the referring clinical colleagues regarding further plan of action.

CT Protocol

- Topography
- CT scans were performed with 120 effective mAs and 130 Kv with a slice thickness of 5mm.

- CT scan images were initially obtained without giving intra venous contrast from the dome of the diaphragms to the symphysis pubis.
- CT renal angiography (diaphragmatic domes to aortic bifurcation) was done using 120 ml of intra venous non-iodinated contrast media at a rate of 4ml per second using a pressure injector.
- A trigger was placed in the descending thoracic aorta. The scan was started when 40 ml of contrast had reached the aorta.
- Nephrographic phase or the venous phase imaging was done from the dome of the diaphragm to the pubic symphysis. This scan was started after a delay of 60-75 seconds.
- After twenty minutes a delayed plain radiograph of the kidney, ureter and bladder was taken.
- Finally coronal and sagittal multiplanar reformats of the kidneys were reconstructed.

The intra venous contrast medium that was used in the study was Iohexol. The dose of contrast medium and the timing of imaging was constant for all participants.

Sequences And Methodology

Relative function of each kidney was determined by each of the four methods described in earlier in the bibliography section. Mean attenuation capacity of the kidney; renal volume; renal length, width and thickness from multi planar reconstructions, parenchymal area estimation was performed by a single observer on Siemens workstation.

In addition the time taken for each CT method per patient was noted. The imaging results was viewed and interpreted by the principal investigator with the help of a co-investigator with experience in abdominal imaging. The observers were blinded to patient's clinical data and renal scintigraphy reports. The data was recorded on the proforma (Appendix 1).

Method 1: Semi-Automated Renal Volume

In this method manual region of interest was drawn around the kidney in such a way to include normal renal parenchyma and exclude non- functioning areas like renal sinus fat, pelvis, calcifications and cysts. Using commercial software volume within the region of interest was derived. Hence volume of both kidneys within the region of interest was obtained separately. The relative volume of each kidney was then be calculated as renal volume divided by the total renal volume of both kidneys.

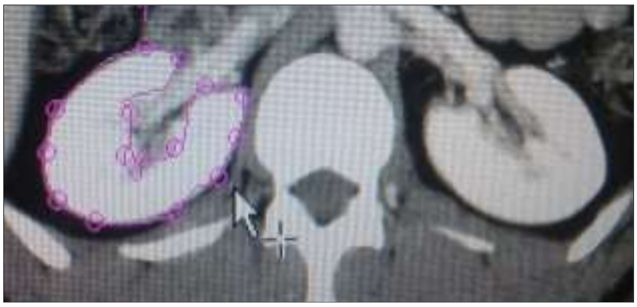

Fig 1: Method 1- Intra venous contrast enhanced CT axial sections of the abdomen at the level of the kidneys demonstrating manually corrected region of interest drawn on the right kidney as in Relative renal volume method. Note that the ROI includes normal enhancing renal parenchyma and excludes hilar fat and blood vessels.

Method 2: Attenuation Capacity

First semi-automated volumes of the kidneys were derived as in method 1. The attenuation value of the kidney was determined by drawing region of interest around the renal contour in each slice as in method 1; mean attenuation value of kidney is displayed automatically after the entire ROI is drawn. The venous phase corresponds to the nephrographic phase of the kidney and is chosen to determine the attenuation capacity of the kidney. Attenuation capacity was then be calculated by multiplying the volume derived by method 1 with the mean attenuation value of each kidney. The relative attenuation capacity of each kidney was obtained dividing attenuation capacity of one kidney by the sum of attenuation capacity of both kidneys.

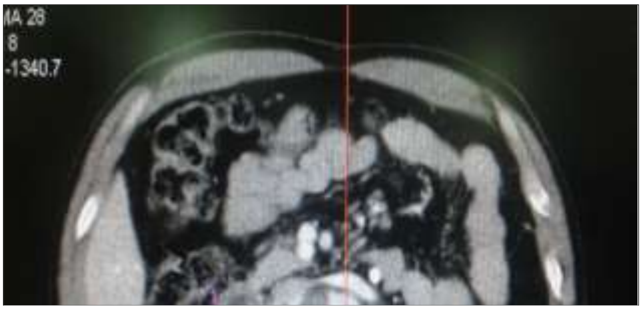

Fig 2: Method 2 - Intra venous contrast enhanced CT axial sections of the abdomen at the level of the kidneys demonstrating manually corrected region of interest drawn on the right kidney as in Relative Mean Attenuation Capacity Method. Note that the color shaded area includes normal enhancing renal parenchyma and excludes hilar fat and blood vessels.

Method 3: Modified Ellipsoid Volume

The ellipsoid volume is defined as length x breadth x thickness x (Pi/6). These measurements were obtained from sagittal and coronal maximum intensity projections.

Length and width was derived from coronal images whereas thickness was measured from the sagittal plane. Measurements used 3 cm maximum intensity projections oriented along the true long axis of each kidney. Oblique MIP images were obtained to maximize the renal length, breath and thickness. Width and thickness were measured at the level of the renal hilum. The relative modified ellipsoid volume of each kidney was obtained by dividing volume of each kidney with the sum of volumes of both kidneys.

Fig 3: Method 3 –Multi planar coronal reformatted images of both the kidneys shows measurement of length and breadth of both the kidneys as in Relative Modified Ellipsoid Volume Method.

Fig 4: Method 3 – Multi planar sagittal reformatted images of the kidney shows measurement of thickness as in Relative Modified Ellipsoid Volume Method. Note that the measurement is taken by drawing a line through the renal hilum.

Method 4: Parenchyma Area

The average parenchymal thickness for each kidney was defined as the mean of six thickness values. Of these 6 values three were taken at the upper pole and three at the lower pole. These values were taken from axial images in the cut where the collecting system had just started to appear. Three measurements were taken from each pole by drawing lines from the margins of the collecting system to the adjacent cortical margins.

The renal length was measured as in method 3.The parenchymal area is defined as the product of average parenchymal thickness and renal length. The relative parenchymal area of each kidney was obtained dividing parenchymal area of each kidney with the sum of parenchymal area of both kidneys.

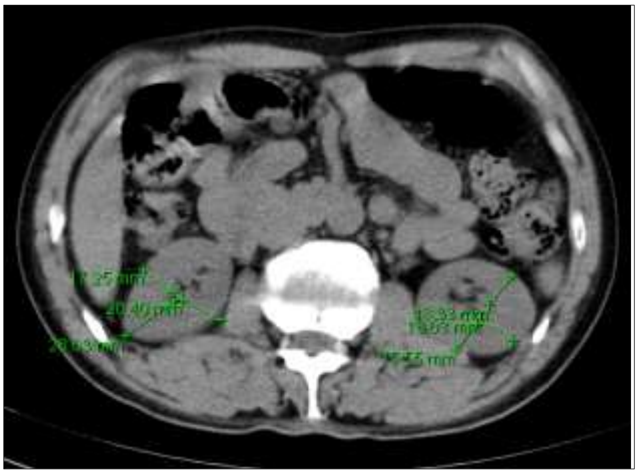

Fig 5: Method 4 – Axial pre contrast CT sections of the abdomen at the level of lower pole of both the kidney where the collecting systems have just appeared, shows measurement of three values (anterior-inferior, posterior-inferior and inferior-lateral) of both the kidneys as in Relative Mean Parenchymal Area Method.

Determination of split renal function by nuclear scintigraphy

The reference standard is Tc99m DTPA renal scintigraphy which is done in the department of nuclear medicine at a nearby DDRC Lab, Bikaner Junction. According to the current protocol for pre-operative evaluation of all potential voluntary kidney donors in these patients undergo a multi-phase contrast enhanced CT for detailed anatomical evaluation and Tc99m DTPA renal scintigraphy for functional assessment (relative function of each kidney). The studies are reviewed and reported by two experienced doctors in the Department of Nuclear Medicine.

The relative renal function and DTPA clearance of each kidney was evaluated according to the method of Gates et al. [44, 45]

The following steps were followed

Technique

The patient was advised optimal hydration with two liters of fluid which was started a couple of hours before the procedure. From the patient's body weight and height the patient's body surface area and mid plane depth of the kidneys are calculated by using the formulae of George and Tonnesen respectively [46, 47]. The mid plane depth of the kidneys can also be determined by ultrasonography or computed tomographic measurements.

The determination of glomerular filtration rate begins with determination of one minute pre-injection syringe count. This value is determined by stirring the count data in 128 x 128 matrixes by placing the radionuclide filled syringe 30 cm from the center of the collimator. After this step the patient is promptly positioned in front of the gamma camera and a bolus of intravenous 99m technetium diethylenetriaminepentaacetic acid (99m Tc DTPA) is given within 1-3 minutes. The usual bolus dose is around 111MBq.

The patient lies supine and the posterior view counts are studied. Acquisition of counts data begins from the time of intravenous bolus injection at the rate of 2 seconds per frame for one minute and fifteen seconds per frame for nineteen minutes thereafter.

After the intravenous bolus of radionuclide is given a one minute post injection syringe count was determined in the same way as the pre injection syringe counts were determined. From the pre and post injection syringe counts the value of net activity can be derived by subtracting the two values.

By adding all eight frames which were acquired at the rate of fifteen seconds per frame for two minutes composite images are acquired. Approximately 50% of the total background count is subtracted to optimize renal identification and is called background correction. This is achieved by drawing region of interests around both the kidneys to assess gross renal counts and semilunar areas of region of interest below both kidneys to assess background counts.

Subsequent step involves the subtraction of background counts from gross renal counts. This gives the net renal activity value which in turn implies the renal activity in both kidneys approximately 2-3 minutes following tracer injection.

After the step of background correction the values are depth corrected using Tonnesen formula (Once depth corrected these values (total renal counts) were then further divided by the net administered syringe counts. This in turn gives the percentage of tracer in each kidney within 2-3 minutes of tracer injection which is also the glomerular filtration rate of each kidney for that tracer. On multiplying this value to the ratio of standard body surface area to body area the value of normalized, GFR is computed.

Finally the total GFR, percentage and relative contribution from both the kidneys are derived.

The relative functional difference between both the kidneys was more than 20%.

Institutional Review Board Approval and Funding

Institutional review board (IRB) approval was obtained prior to the commencement of the Study and the need for informed consent from the patients were waived.

Statistical Analysis

Statistical analyses were performed using SPSS software version 16. For each patient, CT based split renal function estimation was compared to Tc99m DTPA renal scintigraphy results using Intra class correlation test and Pearson's correlation coefficients. Interpretation of *r* values: $r< 0.25$ indicates low correlation, $0.25 <r< 0.5$ indicates moderate correlation, $0.5 <r< 0.75$ Indicates strong correlation, and $r>0.75$ indicates excellent correlation. $P < 0.05$ was considered significant. Bland-Altman plots were drawn to analyze agreement between each CT method and nuclear renal scintigraphy. Box plots were drawn for time taken for each CT method to compare ease of methods and practicality.

Sample Size

Sample size was calculated based on the correlation coefficient (r) reported in a previous study * (Soga et al). Assuming correlation coefficient to be 0.75, with a precision of +/- 0.2 and power of 80% and a syntax level of 5%, a sample size of 65 was required.

Results

Based on the results of our study comparing the four CT based methods of assessing relative renal function with the reference renal Tc99m DTPA scintigraphy, we found an excellent correlation coefficient which was statistically significant (r- 0.79, $p< 0.001$) for the Relative Mean Ellipsoid Volume (RMEV) method with the reference standard.

We also found good correlation coefficients which was statistically significant for Relative Renal Volume (RRV) and Relative Renal Attenuation Capacity (RAC) methods (r-0.757 and 0.742 respectively, $p< 0.001$).

We report only a moderate correlation coefficient which was statistically significant for the Relative Renal Parenchymal Area (RPA) method (r-0.58, $p< 0.001$).

We also report a good agreement for the first three methods with reference renal Tc99m DTPA scintigraphy based on the Bland-Altman analysis. Based on the analysis the first three CT methods (RRV, RAC and RMEV) had width of 95% confidence interval less than 1 (0.76, 0.84 and 0.78 respectively) with a standard deviation of 3-3.3.

Among the CT based methods Relative Renal Parenchymal Area (RPA) method had the least agreement with reference renal Tc99m DTPA scintigraphy. The width of 95% confidence interval was more than 1 (1.08) with a standard deviation of 4.28.

The mean time taken was the least for method 3 or Relative Mean Ellipsoid Volume method which was approximately 3 minutes, which may be attributed to the technical simplicity of deriving only three values for each kidney (length, breadth and thickness).

The mean time taken was the maximum for methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), which may be attributed to the relative technical difficulty in drawing manually corrected region of interests on each slice.

Based on these findings we infer that Method 3 or Relative Mean Ellipsoid Volume Method in terms of its highest correlation coefficient, very good agreement with the reference standard, technical simplicity and least time taken among the other CT methods is the best among the four CT methods to assess relative renal function. In view of the simplicity we recommend that this test can in fact be performed by the referring physician itself.

We also infer that methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), though have a very good correlation with the reference standard are limited due to the technical complexity requiring a workstation monitor and increased time consumption. However these methods score over Relative Mean Ellipsoid Volume method in evaluating subjects with large polar cysts. Using Relative Renal Volume and Relative Renal Attenuation Capacity methods we could carefully exclude these cysts by drawing appropriate manually corrected region of interests.

Fig 6: Intravenous contrast enhance axial CT sections of the kidneys in the venous phase shows carefull exclusion of the right renal upper polar cyst by drawing manual corrected region of interests in Relative Renal Volume method.

Another interesting inference is that methods 1 and 2 (Relative Renal Volume and Relative Renal Attenuation Capacity methods), not only do they have a very good correlation with the reference standard but also have an excellent correlation (r-0.98, $p< 0.001$) amongst themselves. Hence, we can infer that calculation of volume alone is a good parameter in assessing relative renal function and can obviate the need for intra venous contrast enhanced scans in specific clinical scenarios.

We also report that method 4 or Relative Renal Parenchymal Area method is the least favourable in terms of lower correlation coefficient with reference standard (r-0.57, $p< 0.001$), mean time of ~ 12 minutes (SD-2.4) and least agreement with reference standard as compared to the first three CT methods. This method also cannot be applied to subjects with polar cysts.

We acknowledge that the correlation coefficients for this method in our study are much lower than what was reported in some previous studies which was as high as r-0.959 [43]. However, that previous study included subjects with obstructive uropathy which may explain the difference.

Conclusion

1. Computed tomography (CT) due to its excellent anatomical information is an established imaging modality in the pre-operative evaluation of live potential voluntary kidney donors. Intravenous non-iodinated contrast enhanced CT of the abdomen is the current radiological investigation of choice in planning for surgery in such patients.
2. When it comes to functional assessment of live potential voluntary kidney donors renal Tc99m DTPA scintigraphy is considered a reference standard though not the gold standard. A difference of up to 7% of relative renal function does not necessarily mean significant renal functional loss. A functional difference of20% is needed to label a kidney as dominant as compared to the other kidney.
3. CT based methods of assessing relative renal function is an emerging modality and a few of these methods (Relative Renal Volume, Relative Mean Attenuation Capacity and Modified Relative Mean Ellipsoid Volume methods) are useful in assessing relative renal function prior to renal harvest surgery. The quantitative parameters assessed in these methods are the renal volume, mean attenuation capacities and mean ellipsoid volumes.
4. There is excellent correlation (r-0.79, $p< 0.001$) and very good agreement of the Modified Relative Mean Ellipsoid Method with reference renal Tc99m DTPA scintigraphy. Additionally in view of technical simplicity and the least time taken among various other methods, it can be hypothesized that this method is the most practical method to be implemented in day to day practice.
5. Though Relative Renal Volume and Relative Mean Attenuation Capacity methods also show very good correlation with reference renal Tc99m DTPA scintigraphy they are time consuming and technically more difficult as compared to Modified Relative Mean Ellipsoid Method. However they are superior to Relative Mean Ellipsoid Method in the setting of evaluation of subjects with large polar cysts.
6. Relative Renal Volume and Relative Mean Attenuation Capacity methods amongst themselves show a very high correlation (r>0.9). Hence we can hypothesize that volume alone (though it inherently does not include perfusion and renal clearance of intravenous contrast) is sufficient to assess relative renal function in the setting of voluntary renal donation.
7. The Relative Parenchymal Area method has the least correlation coefficient and agreement with the reference standard among the other CT methods assessed in this study. Also, this method cannot be applied in the setting of a subject with large polar cysts.
8. In conclusion, with some CT based methods of assessing relative renal function in the setting of live voluntary kidney donors showing great promise in terms of reliability and applicability CT can be a one stop imaging modality and can replace renal scintigraphy in preoperative evaluation of such patients.

In daily practice, Modified Relative Mean Ellipsoid Volume method can be used in most subjects to assess relative renal function in live voluntary potential kidney donors.

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